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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US98/21609 (22) International Filing Date: 14 October 1998 (14.10.98) (30) Priority Data: 08/950,818 15 October 1997 (15.10.97) US 09/161,653 28 September 1998 (28.09.98) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventors: RAVEENDRANATH, Panolil; 2 Whitman Place, Monroe, NY 10950 (US). ZELDIS, Joseph; 195 Long Clove Drive, New City, NY 10956 (US). VID, Galina; 47 Normandy Village, #2, Nanuet, NY 10954 (US). POTOSKI, John, Richard; 3 Harshorn Lane, West Nyack, NY 10994 (US). REN, Jianxin; 69 Gordon Avenue, Tenafly, NJ 07670 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: NOVEL ARYLOXY-ALKYL-DIALKYLAMINES</p> <div style="text-align: center;"> </div> <p>(57) Abstract</p> <p>The present invention provides compounds useful in the synthesis of biologically active compounds, and processes for their production, the compounds having formula (I) wherein: R¹ and R² are, independently, selected from H; C₁-C₁₂ alkyl or C₁-C₆ perfluorinated alkyl; X represents a leaving group; A is O or S; m is an integer from 1 to 3, preferably 2; R³, R⁴, R⁵, and R⁶ are independently selected from H, halogen, -NO₂, alkyl, alkoxy, C₁-C₆ perfluorinated alkyl, OH or the C₁-C₄ esters or alkyl ethers thereof, -CN, -O-R¹, -O-Ar, -S-R¹, -S-Ar, -SO-R¹, -SO-Ar, -SO₂-R¹, -SO₂-Ar, -CO-R¹, -CO-Ar, -CO₂-R¹, or -CO₂-Ar; and Y is selected from a) the moiety (i) wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl; or b) an optionally substituted five-, six- or seven-membered saturated, unsaturated or partially unsaturated heterocycle or bicyclic heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_n-.</p>		

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NOVEL ARYLOXY-ALKYL-DIALKYLAMINES

This invention provides novel compounds useful in the production of biologically active compounds, as well as processes for their production. More particularly, the present invention provides novel aryloxyalkyl-dialkylamines which may be used in the production of pharmaceutical products.

Background of the Invention

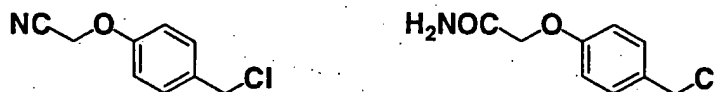
Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes [Woessner, J.F., Jr. *FASEB J.* 1991, 5, 2145; Birkedal-Hansen, H.; Moore, W.G.I.; Bodden, M.K.; Windsor, L.J.; Birkedal-Hansen, B.; DeCarlo, A.; Engler, J.A. *Crit. Rev. Oral Biol. Med.* 1993, 4, 197; Cawston, T.E. *Pharmacol. Ther.* 1996, 70, 163; Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* 1996, 213, 1]. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. Of these classes, the gelatinases have been shown to be the MMPs most intimately involved with the growth and spread of tumors, while the collagenases have been associated with the pathogenesis of osteoarthritis [Howell, D.S.; Pelletier, J.-P. In *Arthritis and Allied Conditions*; McCarthy, D.J.; Koopman, W.J., Eds.; Lea and Febiger: Philadelphia, 1993; 12th Edition Vol. 2, pp. 1723; Dean, D.D. *Sem. Arthritis Rheum.* 1991, 20, 2; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* 1994-95, 14, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, 1996, 5, 323].

The use of hormone replacement therapy for bone loss prevention in post-menopausal women is well precedented. The normal protocol calls for estrogen supplementation using such formulations containing estrone, estriol, ethynyl estradiol or conjugated estrogens isolated from natural sources (i.e. Premarin® conjugated estrogens from Wyeth-Ayerst). In some patients, therapy may be contraindicated due to the proliferative effects unopposed estrogens (estrogens not given in combination with progestins) have on uterine tissue. This proliferation is associated with increased risk for endometriosis and/or endometrial cancer. The effects of unopposed estrogens on breast tissue is less clear, but is of some concern. The need for estrogens which can

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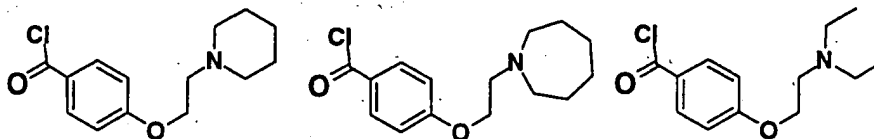
maintain the bone sparing effect while minimizing the proliferative effects in the uterus and breast is evident. Certain nonsteroidal antiestrogens have been shown to maintain bone mass in the ovariectomized rat model as well as in human clinical trials. Tamoxifen (sold as Novadex[®] brand tamoxifen citrate by Zeneca Pharmaceuticals, Wilmington, Delaware), for example, is a useful palliative for the treatment of breast cancer and has been demonstrated to exert an estrogen agonist-like effect on the bone, in humans. However, it is also a partial agonist in the uterus and this is cause for some concern. Raloxifene, a benzthiophene antiestrogen, has been shown to stimulate uterine growth in the ovariectomized rat to a lesser extent than Tamoxifen while maintaining the ability to spare bone. A suitable review of tissue selective estrogens is seen in the article "Tissue-Selective Actions Of Estrogen Analogs", *Bone* Vol. 17, No. 4, October 1995, 181S-190S.

The present invention provides novel intermediates which may be used in the production of pharmaceutical compounds for anti-estrogenic and MMP-inhibiting utilities. The use of 4-carbamoylmethoxy-methoxy-benzyl chloride compounds of the structures:



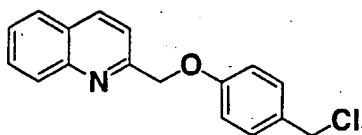
are taught in NL 6402393; 1964; and Chem. Abstr. 1965, 62, 7698.

The use of 4-(2-dialkylamino-ethoxy)benzoyl chloride compounds of the structures:



are disclosed in Sharpe, C. J. et.al. J. Med. Chem. 1972, 15, 523 and Jones, C. D. et.al. J. Med. Chem. 1984, 27, 1057. Similarly, the use of 4-(2-quinolinylmethoxy)benzyl chloride

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is disclosed by Huang, F-C. et. al. J. Med. Chem. 1990, 33, 1194.

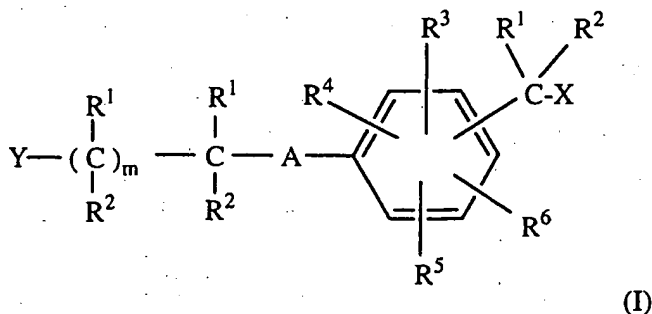
Summary of the Invention

5

The present invention provides new compounds, as well as methods for the production thereof, which can be used in the production of pharmaceutically active compounds. The compounds of this invention can particularly be used as intermediates in the production of pharmaceutical compounds, such as low molecular weight, non-peptide inhibitors of matrix metalloproteinases (e.g. gelatinases, stromelysins and collagenases) and TNF- α converting enzyme (TACE, tumor necrosis factor- α converting enzyme) which are useful for the treatment of diseases in which these enzymes are implicated such as arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system and HIV infection. In addition, the compounds of this invention can be used to produce compounds which behave like estrogen agonists by lowering cholesterol and preventing bone loss. Therefore, these compounds are useful for treating many maladies including osteoporosis, prostatic hypertrophy, infertility, breast cancer, endometrial hyperplasia and cancer, cardiovascular disease, contraception, Alzheimer's disease and melanoma.

20

The present invention includes novel compounds of formula (I):

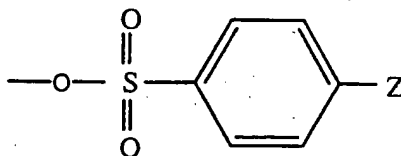


25 wherein:

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R^1 and R^2 are, independently, selected from H; C_1 - C_{12} alkyl, preferably C_1 - C_6 alkyl; or C_1 - C_6 perfluorinated alkyl, preferably $-CF_3$;

X is a leaving group, such as halogen, $-O-SO_2-CH_3$, $-O-SO_2-CF_3$, or a moiety
5 of the structure:



Z is selected from $-NO_2$, halogen, $-CH_3$ or $-CF_3$;

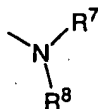
A is selected from $-O-$ or $-S-$, $-SO-$ or $-SO_2-$;

m is an integer from 0 to 3, preferably 1;

10 R^3 , R^4 , R^5 , and R^6 are independently selected from H, halogen, $-NO_2$, alkyl (preferably C_1 - C_{12} alkyl, more preferably C_1 - C_6 alkyl), alkoxy (preferably C_1 - C_{12} alkoxy, more preferably C_1 - C_6 alkoxy), C_1 - C_6 perfluorinated alkyl (preferably $-CF_3$), OH or the C_1 - C_4 esters or alkyl ethers thereof, $-CN$, $-O-R^1$, $-O-Ar$, $-S-R^1$, $-S-Ar$, $-SO-R^1$, $-SO-Ar$, $-SO_2-R^1$, $-SO_2-Ar$,
15 $-CO-R^1$, $-CO-Ar$, $-CO_2-R^1$, or $-CO_2-Ar$;

Y is selected from:

a) the moiety:



20 wherein R^7 and R^8 are independently selected from the group of H, C_1 - C_6 alkyl, or phenyl.

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of $-O-$, $-NH-$, $-N(C_1C_4 \text{ alkyl})-$, $-N=$, and $-S(O)_n-$, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group
25 consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, phenyl optionally substituted with 1-3 (C_1 -

- 5 -

C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

5 c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

15 d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂; or

20 e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

30 and the pharmaceutically acceptable salts thereof.

It is understood in the generic description above and the other groups herein that, in each instance they may appear, R¹ and R² are independently selected from the group of substituents listed. Any R¹ listed in any structure herein need not represent

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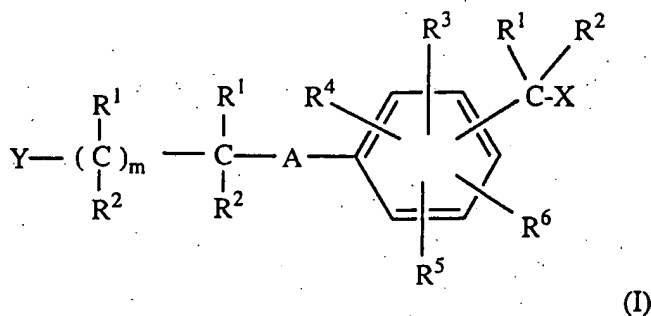
the same substituent as another R^1 , nor does any R^2 have to be the same substituent as any other R^2 , even if more than one R^1 or R^2 are found in the same structure.

5 In the description above, the symbol "Ar" indicates an monocyclic or polycyclic aryl or heteroaryl groups which may be optionally substituted by one or more substituents selected from halogen, C_1 - C_6 alkyl or $-CF_3$. Examples of preferred aryl groups include anthracenyl, and phenanthrenyl groups, as well as the more preferred phenyl, cumenyl, mesityl, tolyl, xylyl, and naphthalenyl groups. Examples of preferred heteroaryl groups include indoliziny, indazolyl, indazolyl, purinyl, 10 quinoziny, isoquinolinyl, quinolinyl, phthalozinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, and pteridinyl groups, and the like, as well as the more preferred pyridyl, pyrazinyl, pyrimidinyl, pyridiziny and indolyl groups.

15 The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. 20 It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and not protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein, which can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive 25 alkylating agent such as an alkyl halide or benzyl halide.

Among the preferred compounds of this invention are those of the formula (I):

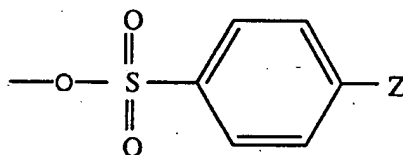
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wherein:

R¹ and R² are, independently, selected from H; C₁-C₁₂ alkyl, preferably C₁-C₆ alkyl; or C₁-C₆ perfluorinated alkyl, preferably -CF₃;

5 X is a leaving group, such as halogen, -O-SO₂-CH₃, -O-SO₂-CF₃, or a moiety of the structure:



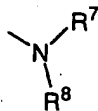
Z is selected from -NO₂, halogen, -CH₃ or -CF₃;

A is selected from -O- or -S-, -SO- or -SO₂-;

10 m is an integer from 0 to 3, preferably 1;

Y is selected from:

a) the moiety:



15 wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl.

b) a group selected from thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, isoxazole, or oxathiolane, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, 20 C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -

CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

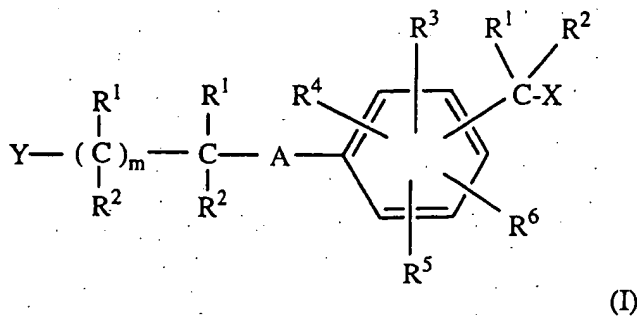
5 c) a group selected from pyridine, pyrazine, pyrimidine, pyridazine, piperidine, morpholine and pyran, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino,
10 -NHSO₂R¹, -NHCOR¹, -NO₂;

d) a group selected from azepine, diazepine, oxazepine, thiazepine, oxapin and thiepin, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio,
15 C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂; or

e) a bicyclic heterocycle selected from the group of benzofuran, isobenzofuran, benzothiophene, indole, isoindole, indolizine, indazole, purine,
20 quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, and cinnoline, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally
25 substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;
and the pharmaceutically acceptable salts thereof.

Further preferred compounds of this invention are those of the formula (I):

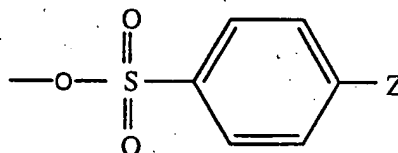
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wherein:

R¹ and R² are, independently, selected from H; C₁-C₁₂ alkyl, preferably C₁-C₆ alkyl; or C₁-C₆ perfluorinated alkyl, preferably -CF₃;

5 X is a leaving group, such as halogen, -O-SO₂-CH₃, -O-SO₂-CF₃, or a moiety of the structure:



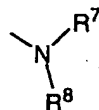
Z is selected from -NO₂, halogen, -CH₃ or -CF₃;

A is selected from -O- or -S-, -SO- or -SO₂-;

10 m is an integer from 0 to 3, preferably 1;

Y is selected from:

a) the moiety:



15 wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl; or

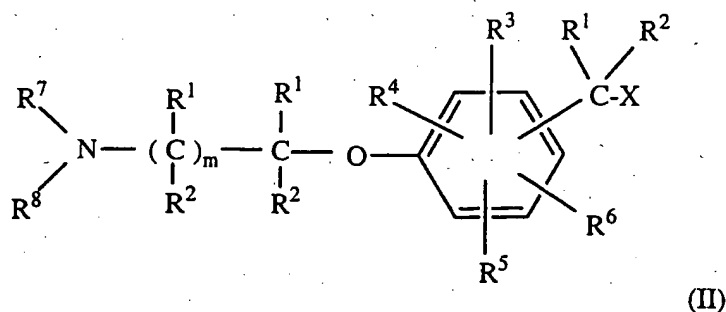
b) a group selected from thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, indole or benzofuran, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally

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substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂; and the pharmaceutically acceptable salts thereof.

- 5 Among the more preferred compounds of the present invention are those having the general formula



wherein:

- 10 R¹ and R² are, independently, selected from H, C₁-C₆ alkyl or C₁-C₆ perfluorinated alkyl, preferably, among the perfluorinated alkyl groups, -CF₃;

R³, R⁴, R⁵, and R⁶ are independently selected from H, OH or the C₁-C₄ esters or alkyl ethers thereof, halogen, -CN, C₁-C₆ alkyl, or trifluoromethyl,

m is an integer from 0 to 3, preferably 1;

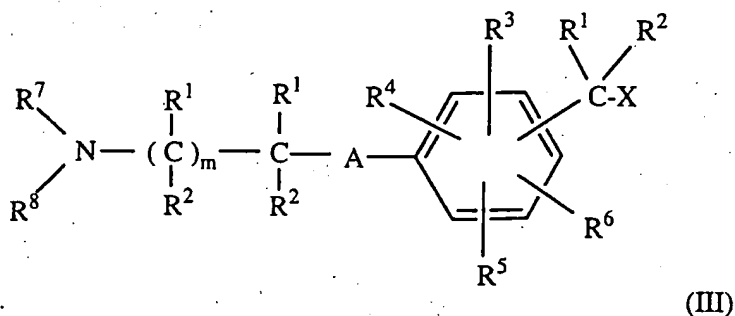
- 15 R⁷ and R⁸ are selected independently from H, C₁-C₆ alkyl, or combined by - (CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₃; and

20 X is as defined above;

and the pharmaceutically acceptable salts thereof.

- 25 Also among the more preferred compounds of the present invention are those having the general formula

- 11 -



wherein:

R^1 and R^2 are, independently, selected from H, C_1 - C_6 alkyl or C_1 - C_6 perfluorinated alkyl, preferably, among the perfluorinated alkyl groups, $-CF_3$;

5 R^3 , R^4 , R^5 , and R^6 are independently selected from H, OH or the C_1 - C_4 esters or alkyl ethers thereof, halogen, $-CN$, C_1 - C_6 alkyl, or trifluoromethyl,

m is an integer from 0 to 3, preferably 1;

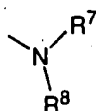
A is selected from $-S-$, $-SO-$ or $-SO_2-$;

R^7 and R^8 are selected independently from H, C_1 - C_6 alkyl, or combined by -
 10 $(CH_2)_p$ -, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$, $-CN$, $-CONH(C_1-C_4)$, $-NH_3$, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, $-NHSO_2(C_1-$
 15 $C_4)$, $-NHCO(C_1-C_4)$, and $-NO_2$; and

X is as defined above;

and the pharmaceutically acceptable salts thereof.

20 Among the most preferred compounds of the present invention are those having the structural formulas II or III, above, wherein R^3 - R^6 are as defined above; X is selected from the group of Cl, $-CF_3$, or $-CH_3$; and Y is the moiety



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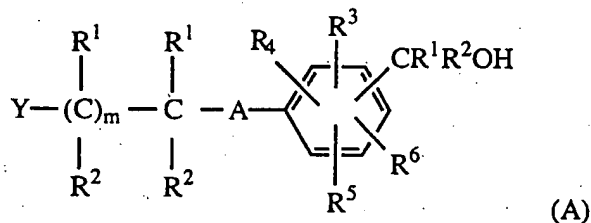
and R^7 and R^8 are concatenated together as $-(CH_2)_r-$, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy
 5 $(C_1$ - C_4)alkyl, $-CO_2H$, $-CN$, $-CONH(C_1-C_4)$, $-NH_3$, C_1 - C_4 alkylamino, C_1 - C_4 dialkylamino, $-NHSO_2(C_1-C_4)$, $-NHCO(C_1-C_4)$, and $-NO_2$;
 and the pharmaceutically acceptable salts thereof.

It is further preferred that, when R^7 and R^8 are concatenated together as -
 10 $(CH_2)_p$ - or $-(CH_2)_r$ -, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C_1 - C_3 alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, $-CN$.

This invention also includes a process for making the compounds above.

15 The compounds of the invention may be prepared by a process comprising one of the following:

a) converting an alcohol of formula



20

wherein m , A , Y and R^{1-6} are as defined above

to a corresponding compound of formula I wherein X is a leaving group by appropriate means; e.g using a halogenating, sulfonylating or acylating agent containing the
 25 leaving group X ;

or

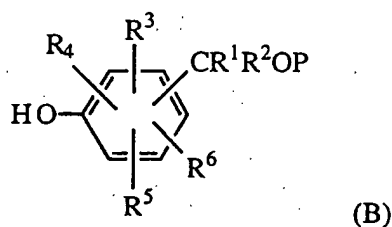
b) oxidising a compound of formula I wherein A is S to give a corresponding compound of formula I wherein A is SO or $-SO_2-$.

or

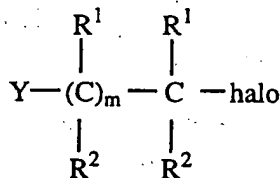
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c) converting a compound of formula (I) to a pharmaceutically acceptable salt thereof.

5 Compounds of formula (A) can be prepared by reacting a phenol of formula



10 wherein P is a hydroxy protecting group and R¹⁻⁶ are as defined above (e.g R¹ and R² are each H or C₁-C₁₂ alkyl) with a compound of formula

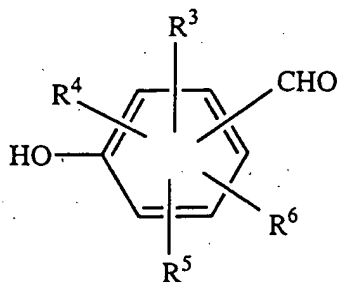


15 wherein Y, R¹, R² and m are as defined above and halo is F, Cl, Br or I and removing the protecting group.

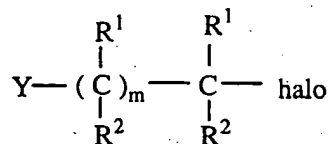
Compounds of this invention in which "A" is oxygen can be synthesized by the process steps of:

20 a) alkylating a relevant hydroxybenzaldehyde of the formula:

- 14 -

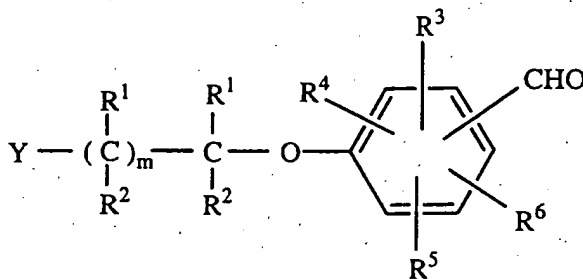


wherein R^3 - R^6 are as defined above, with a relevant alkyl halide of the formula:

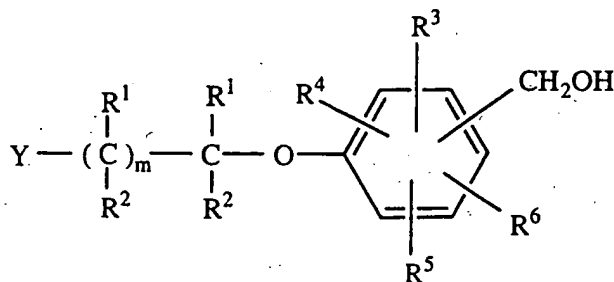


wherein Y, R^1 , R^2 and m are as defined in the generic and subgeneric groups above and

5 halo can be Cl, F, Br or I, to produce an aldehyde of the formula:



b) reducing the aldehyde product of step a), to yield the relevant alcohol having a formula:



10 c) converting the alcohol of step b) to its hydrochloride salt, such as with HCl/THF; and

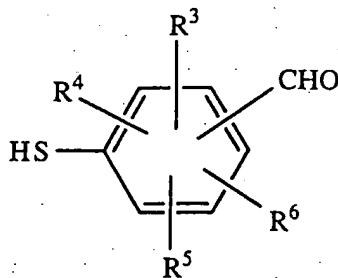
- 15 -

d) converting the alcohol to a preferred leaving group, such as through treatment with methanesulfonyl chloride, toluenesulfonyl chloride, or trifluoroacetic anhydride in the presence of a base like pyridine or triethylamine.

5

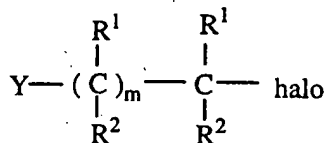
Similarly, the present invention provides a process for producing compounds of this invention wherein "A" is sulfur through the steps of:

a) alkylating a compound of the formula

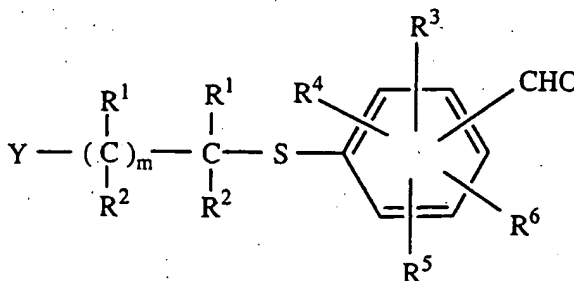


10

with an alkylating agent of the formula:



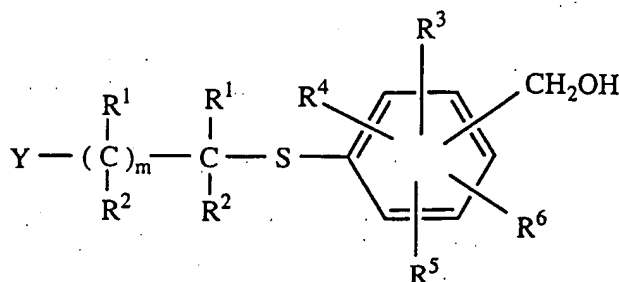
wherein Y and m are as defined above and halo is selected from Cl, F, Br or I, to produce an aldehyde of the formula:



15

b) reduction of the aldehyde product of step a), such as with sodium borohydride, to an alcohol of the formula;

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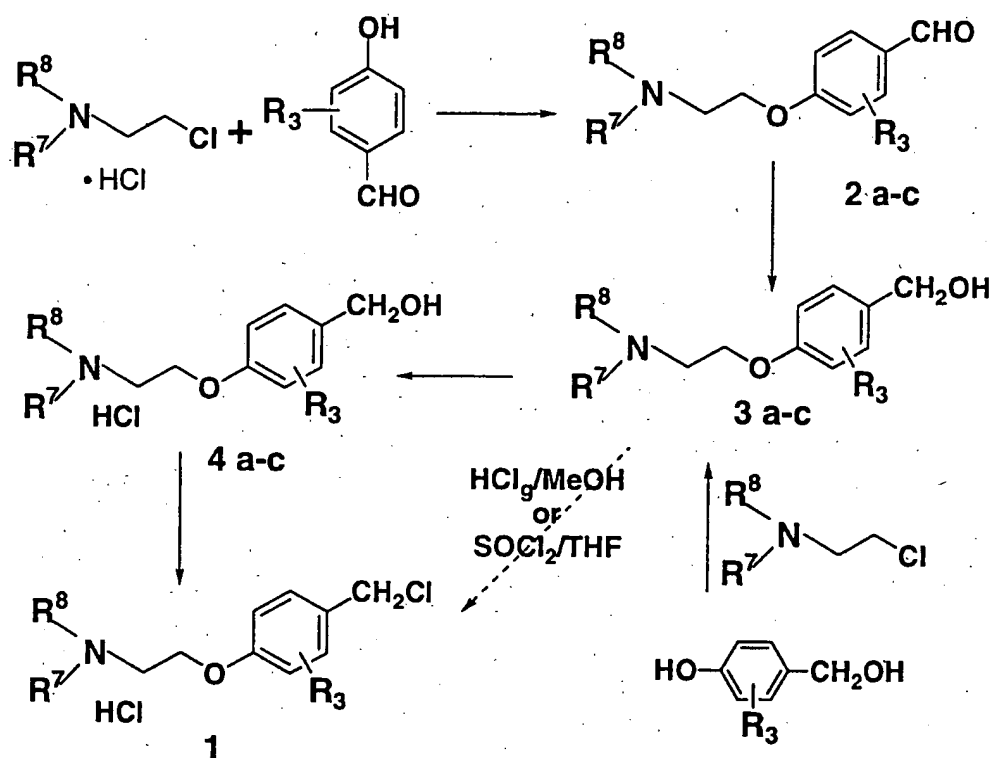
- c) treatment of the alcohol of step b) with gaseous HCl to generate its hydrochloride; and
- d) converting the alcohol hydrochloride product of step c) to a preferred leaving group, such as through treatment with methanesulfonyl chloride, toluenesulfonyl chloride, or trifluoroacetic anhydride in the presence of a base like pyridine or triethylamine or continued treatment with HCl to form the corresponding benzyl chloride; and,
- e) optionally, completing controlled oxidation of the sulfur to sulfoxide or to sulfone, such as with m-chloroperbenzoic acid.

The starting thiophenoxide aldehyde material of step a), above, may be generated from its corresponding thiophenol aldehyde, such as with sodium hydride, which may or may not be considered a step of the process, above.

Detailed Description of the Invention

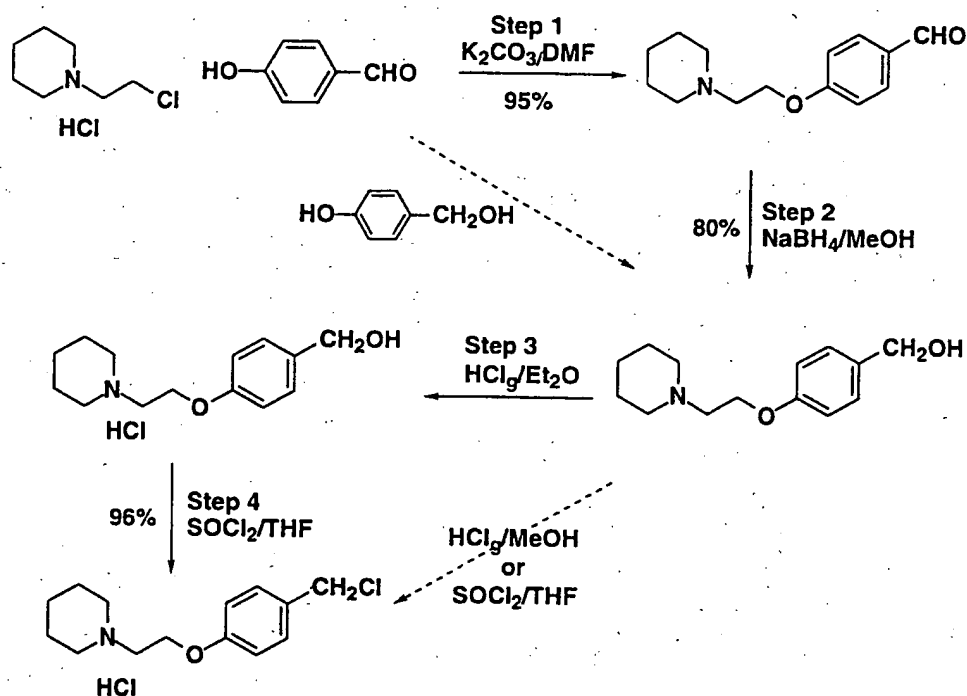
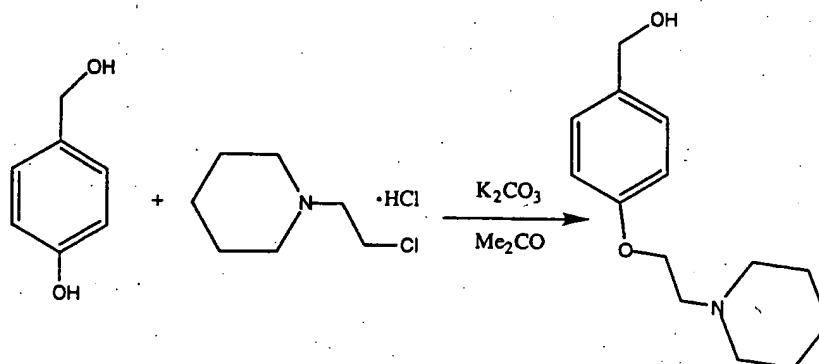
The following reactions Schemes I through IV demonstrate the synthesis of compounds of the present invention, utilizing different variables for "Y". The reagents and solvents for the individual steps are given for illustrative purposes only and may be replaced by other reagents and solvents known to those skilled in the art.

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Scheme I

a, R⁷R⁸ = (CH₂)₅; b, R⁷R⁸ = (CH₂)₆; c, R⁷ = R⁸ = CH₃ and R₃ = H.

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Scheme IIScheme IIa

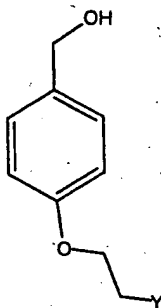
5

Scheme IIa offers an alternative synthesis of the benzyl alcohols of this invention, exemplifying the synthesis of 4-(2-piperidinylethoxy)benzyl alcohol. In this synthesis 4-hydroxybenzyl alcohol is treated with a desired aryl amino-alkyl chloride to

- 19 -

afford the corresponding alkoxy benzyl alcohol. In the specific example of Scheme IIa, 4-hydroxybenzyl alcohol can be treated with 1-(2-chloroethyl)-piperidine hydrochloride in the presence of K_2CO_3/Me_2CO to yield 4-(2-piperidinyloxy)benzyl alcohol.

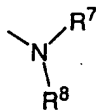
- 5 Scheme IIa also more specifically illustrates another preferred embodiment of the present invention. This invention also includes a process for producing useful alcohol compounds of the formula:



- 10 wherein Y represents the Y groups and their optional substituents as described most generically above.

In a preferred subgroup of this process, Y represents:

- a) the moiety



15

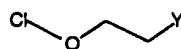
wherein R7 and R8 are independently selected from the group of H, C₁-C₆ alkyl, or phenyl; or

- 20 b) a five-, six- or seven-membered unsaturated or partially unsaturated heterocyclic ring containing one or two nitrogen atoms, the heterocyclic ring being bound to the ethoxy bridge at a nitrogen atom in the ring and being optionally substituted by from 1 to 3 groups selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ thioalkyl, -CF₃, or -NO₂.

- 20 -

Among the preferred Y groups of this process are azepine, pyrrole, imidazoline, imidazolidine, hexamethyleneimine, pyrrolidine, pyrazolidine, pyrazoline, piperidine, piperazine,

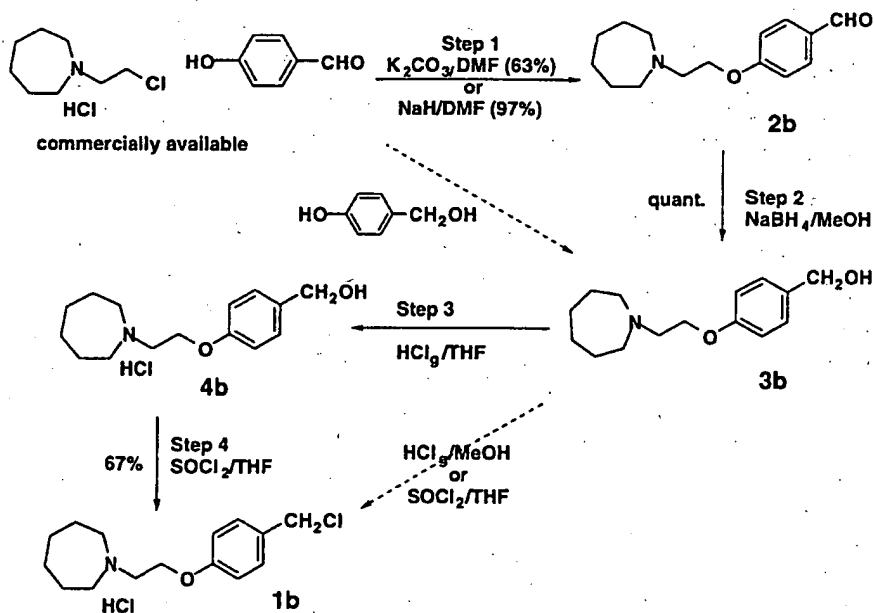
- 5 The process comprises reacting, in an alkaline medium, 4-hydroxybenzyl alcohol with a salt, such as an acetate, hydrochloride, hydrobromide or hydroiodide salt, of a compound of the formula:



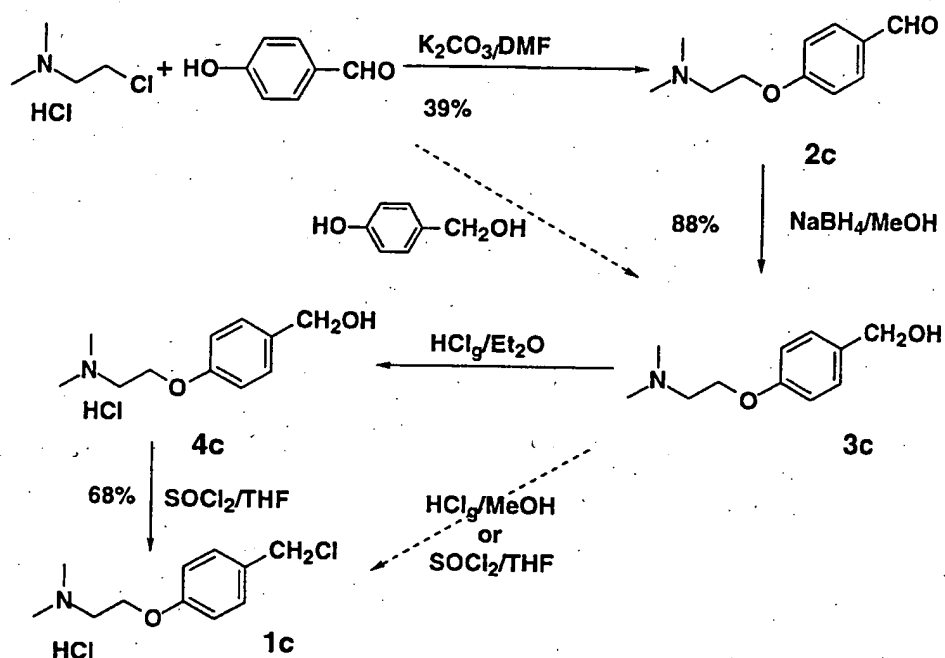
- 10 wherein Y is as defined above.

This reaction is carried out in an organic solvent or solvent system, such as in acetone, dimethylformamide or tetrahydrofuran. Preferably the pH of the medium is maintained above a pH of 8, more preferably above a pH of 9.

15

Scheme III

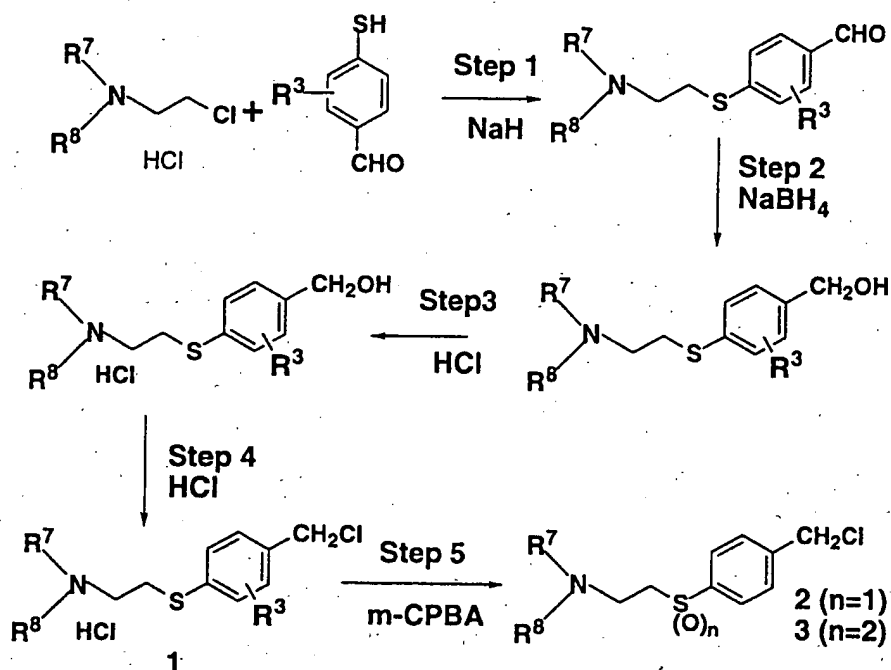
- 21 -

Scheme IV

Utilizing similar steps, compounds of this invention wherein "A" is sulfur may be produced as shown in Scheme V, below. In a first step thiophenoxide may be produced with sodium hydride, followed by alkylation and reduction to the relevant aldehyde, such as with sodium borohydride or catalytically with Hydrogen and Raney Nickel or platinum or palladium on carbon catalysts. The resulting alcohol may then be treated with gaseous HCl to generate its hydrochloride, with continued HCl treatment to form a benzyl chloride. The final product may then be formed by controlled oxidation of the sulfur to sulfoxide, and then to sulfone, such as with m-chloroperbenzoic acid.

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Scheme V



The following examples are presented to illustrate rather than limit the scope of the invention.

- 5 In the procedures above compounds of formula (I) where R¹ and R² adjacent the X moiety represent hydrogen are prepared from primary alcohols (eg Scheme I, compounds 3a-c) which are themselves prepared by reducing aldehyde precursors (eg Scheme I, compounds 2a-c).
- 10 Analogous compounds of formula (I) wherein one of R¹ and R² adjacent the X moiety is alkyl or perfluoroalkyl, and the other is hydrogen, may be prepared from appropriate secondary alcohols which themselves may be prepared from corresponding ketones, eg compounds having a COR¹ moiety where R¹ is alkyl or perfluoroalkyl.
- 15 Analogous compounds of formula (I) wherein both of R¹ and R² adjacent the X moiety are each selected from alkyl and perfluoroalkyl may be prepared from appropriate tertiary alcohols.

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EXAMPLE 1**4-(2-piperidine-1-yl-ethoxy)-benzyl aldehyde (2a)**

5

To a well-stirred slurry of p-hydroxybenzaldehyde (83.5 g, 0.68 mol, 1.05 eq.) and K_2CO_3 (224 g, 1.6 mol, 2.5 eq.) in DMF (1 L), 1-(2-chloroethyl)piperidine hydrochloride (120 g, 0.65 mol, 1.0 eq.) is added. The reaction mixture is refluxed for 2 h with vigorous mechanical stirring. TLC at this point shows no starting material, mostly product (EtOAc/hexane 1:1). The reaction mixture is filtered through Celite, deluted with EtOAc (2 L), and washed with water (3 x 500 mL). The organic layer is concentrated on a rotary evaporator to give 147 g (97 %) of aldehyde (2a) as a yellow oil.

10 1H NMR ($CDCl_3/TMS$): 9.87 (s, 1H), 7.81 (d, 2H, J = 8.7 Hz), 7.01 (d, 2H, J = 8.7 Hz), 4.18 (t, 2H, J = 6.03 Hz), 2.79 (t, 2H, J = 6.03 Hz), 2.51 (m, 4H), 1.6-1.4 (m, 6H)

EXAMPLE 2**4-(2-hexamethyleneimine-1-yl-ethoxy)-benzyl aldehyde (2b)**

20

To a well-stirred slurry of NaH (65 g, 60 % oil dispersion, 1.6 mol, 2.2 eq.) in DMF (500 mL) a solution of p-hydroxybenzaldehyde hydrochloride (90 g, 0.74 mol, 1.0 eq.) is added dropwise at 0 °C. The reaction mixture is stirred for 30 min, then 4-[2-(hexamethyleneimino)]ethylchloride (153 g, 0.77 mol, 1.0 eq.) is added in portions. The reaction mixture is stirred for 1 h. TLC at this point shows little starting material, mostly product (EtOAc/hexane 1:1). The reaction mixture is diluted with water (1 L), and extracted with ether (5 L). The organic layer is dried over $MgSO_4$, and concentrated on a rotary evaporator to give 176.8 g (97 %) of aldehyde (2b) as a yellow oil.

25 1H NMR ($CDCl_3/TMS$): 9.87 (s, 1H), 7.81 (d, 2H, J = 8.7 Hz), 7.02 (d, 2H, J = 8.7 Hz), 4.14 (t, 2H, J = 6.09 Hz), 2.98 (t, 2H, J = 6.14 Hz), 2.78 (m, 4H), 1.66-1.61 (m, 8H)

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EXAMPLE 3**4-(2-dimethylamino-ethoxy)-benzyl aldehyde (2c)**

To a well-stirred slurry of p-hydroxybenzaldehyde (9.54 g, 0.078 mol, 1.00 eq.) and K_2CO_3 (27 g, 0.195 mol, 2.5 eq.) in DMF (100m L), 1-(2-chloroethyl)dimethylamine hydrochloride (11.26 g, 0.078 mol, 1.0 eq.) is added. The reaction mixture is stirred for 2 h at 60 - 70 °C. TLC at this point shows no starting material, mostly product (EtOAc/hexane/ Et_3N 3:7:1). The reaction mixture is poured into water/ice mixture (200 mL), and extracted with Et_2O (3 x 200 mL). The organic layer is dried with $MgSO_4$, and concentrated on a rotary evaporator to give 5.9 g (39 %) of aldehyde (**2c**) as a pinkish liquid.

1H NMR ($CDCl_3/TMS$): 9.88 (s, 1H), 7.8 (d, 2H, $J = 8.7$ Hz), 7.02 (d, 2H, $J = 8.7$ Hz), 4.15 (t, 2H, $J = 5.64$ Hz), 2.77 (t, 2H, $J = 5.64$ Hz), 2.35 (s, 6H).

EXAMPLE 4**4-(2-piperidine-1-yl-ethoxy)-benzyl alcohol (3a)**

To a stirred solution of the aldehyde **2a** (115 g, 0.494 mol, 1.0 eq.) in methanol (360 mL) at 0 / +5 °C sodium borohydride (9.44 g, 0.249 mol, 0.5 eq.) is added in portions. The reaction is stirred for 30 min. TLC at this point shows no starting material, mostly product (EtOAc/hexane/triethylamine 3:7:1). The reaction mixture is poured in water (1.1 L), extracted with methylene chloride (3 x 550 mL), and dried over $MgSO_4$. The solution is concentrated on a rotary evaporator to give 91.6 g (80 %) of the alcohol **3a** as a thick oil which crystallized instantly on seeding.

1H NMR ($CDCl_3/TMS$): 7.23 (d, 2H, $J = 8.5$ Hz), 6.80 (d, 2H, $J = 8.5$ Hz), 4.56 (s, 2H), 3.99 (t, 2H, $J = 6.12$ Hz), 2.69 (t, 2H, $J = 6.14$ Hz), 2.47 (m, 4H), 1.6-1.25 (m, 6H)

^{13}C NMR ($DMSO-d_6$): 158.23, 135.34, 128.70, 114.84, 66.42, 63.44, 58.27, 55.29, 26.45, 24.80

- 25 -

EXAMPLE 5**4-(2-piperidine-1-yl-ethoxy)-benzyl alcohol (3a)**

4-hydroxybenzyl alcohol (6.2 g, 0.05 mol) was dissolved in aqueous sodium hydroxide (5N, 30 mL). Toluene (30 mL) was added followed by 1-(2-chloroethyl)piperidine hydrochloride (9.29 g, 0.05 mol) and benzyltriethylammonium bromide (0.3 g). The reaction mixture was heated with vigorous stirring for 1.5 h. The layers were separated, the aqueous layer was extracted with toluene (2 x 15 mL). Combined organic extracts and organic layer was washed with water (50 mL), brine (50 mL), dried over sodium sulfate, and concentrated on a rotary evaporator to give 8.725 g (75 %) of alcohol (**3a**) as a yellowish brown oil.

EXAMPLE 6**4-(2-hexamethyleneimine-1-yl-ethoxy)-benzyl alcohol (3b)**

To a stirred solution of the aldehyde **2b** (200 g, 0.72 mol, 1.0 eq.) in methanol (400 mL) at 0 / +5 °C sodium borohydride (15.6 g, 0.41 mol, 0.57 eq.) is added in portions. The reaction is stirred for 30 min. TLC at this point shows no starting material, mostly product (EtOAc/hexane/triethylamine 3:7:1). The reaction mixture is diluted with water (400 mL), extracted with methylene chloride (3 x 400 mL), and dried over MgSO₄. The solution is concentrated on a rotary evaporator to give 201 g (100 %) of the alcohol **3b** as a thick oil.

¹H NMR (CDCl₃/TMS): 7.27 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.5 Hz), 4.60 (s, 2H), 4.05 (t, 2H, J = 6.21 Hz), 2.93 (t, 2H, J = 6.15 Hz), 2.77 (m, 4H), 1.7-1.5 (m, 8H).

EXAMPLE 7**4-(2-dimethylamino-ethoxy)-benzyl alcohol (3c)**

To a stirred solution of the aldehyde **2c** (5.9 g, 0.031 mol, 1.0 eq.) in methanol (20 mL) at 22 °C sodium borohydride (0.58 g, 0.015 mol, 0.5 eq.) is added in portions. The reaction is stirred for 30 min. TLC at this point shows no starting material, mostly product (EtOAc/hexane/triethylamine 5:5:1). The reaction mixture is diluted with water (50 mL), extracted with methylene chloride (3 x 40 mL), and dried

- 26 -

over MgSO_4 . The solution is concentrated on a rotary evaporator to give 5.25 g (88 %) of the alcohol **3c** as a thick oil.

^1H NMR (CDCl_3/TMS): 7.25 (d, 2H, $J = 8.64$ Hz), 6.85 (d, 2H, $J = 8.64$ Hz), 4.52 (s, 2H), 3.99 (t, 2H, $J = 5.88$ Hz), 2.67 (t, 2H, $J = 5.79$ Hz), 2.29 (s, 6H)

5

EXAMPLE 8

(4-Chloromethyl-phenoxy)-ethyl-piperidin-1-yl hydrochloride (1a)

A solution of the alcohol **3a** (61.3 g, 0.26 mol, 1 eq.) in THF (500 mL) is cooled to 0 / -5 °C (ice-water bath) and bubbled with gaseous HCl. Bubbling is continued until no more thickening of the reaction mixture occurred. The cooling bath is removed. Thionyl chloride (29 mL, 0.39 mol, 1.5 eq.) is added to the thick slurry of hydrochloride **4a**, and the mixture is heated to 50 °C until clear. The reaction mixture is cooled to -3 °C and stirred for 30 min. The white solid obtained is filtered and dried to give 72 g (96 %) of chloride **1a**.

4a: ^1H NMR ($\text{DMSO}-d_6$): 10.9 (s, HCl), 7.25 (d, 2H, $J = 8.5$ Hz), 6.94 (d, 2H, $J = 8.5$ Hz), 4.42 (m, 4H), 3.41 (m, 4H)

1a: ^1H NMR ($\text{DMSO}-d_6$): 11 (br s, HCl), 7.39 (d, 2H, $J = 8.5$ Hz), 6.99 (d, 2H, $J = 8.5$ Hz), 4.74 (s, 2H), 4.46 (m, 2H), 3.45 (m, 4H), 2.69 (m, 2H) and 1.9-1.2 (m, 6H)

20

EXAMPLE 9

(4-Chloromethyl-phenoxy)-ethyl-hexamethyleneimine-1-yl hydrochloride (1b)

25

To a solution of the alcohol **3b** (179 g, 0.72 mol, 1 eq.) in THF (300 mL) a solution of HCl (26.3 g of HCl in 263 mL of THF, 0.72 mol, 1.0 eq.) is added dropwise at 0 / +10 °C. A white precipitate is formed. Thionyl chloride (80 mL, 1.1 mol, 1.5 eq.) is added to the thick slurry of hydrochloride **4b**, and the mixture is heated to 50 °C until clear. The reaction mixture is concentrated to 350 mL, and kept in refrigerator overnight. The white solid obtained is filtered, washed with cold THF (100 mL), and dried to give 147 g (67 %) of chloride **1b**.

30

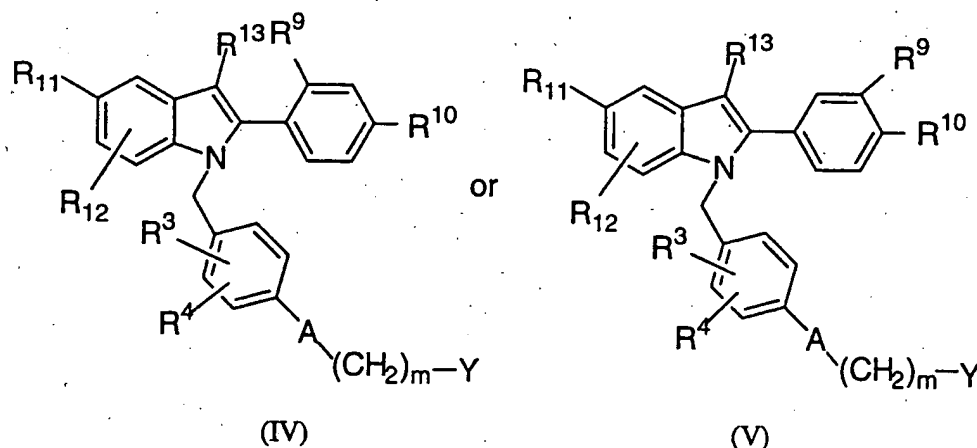
¹H NMR (DMSO-d₆): 11 (br s, HCl), 7.40 (d, 2H, J = 8.6 Hz), 7.00 (d, 2H, J = 8.6 Hz), 4.74 (s, 2H), 4.44 (t, 2H, J = 5.25), 3.64 - 3.39 (m, 4H), 3.25 - 3.17 (m, 2H), 1.84-1.54 (m, 8H)

EXAMPLE 10

(4-Chloromethyl-phenoxy)-ethyl-dimethylamino hydrochloride (1c)

To a solution of the alcohol 3c (5.25 g, 0.027 mol, 1 eq.) in THF (100 mL) gaseous HCl was bubbled at 0 / + 25 °C for 15 min. A white precipitate is formed. Thionyl chloride (6 mL, 9.6 g, 0.081 mol, 3.0 eq.) is added to the thick slurry of hydrochloride 4c, and the mixture is heated to 30 °C until clear. The reaction mixture is concentrated to 350 mL, and kept in refrigerator overnight. The white solid obtained is filtered, washed with cold THF (100 mL), and dried to give 4.57 g (68 %) of chloride 1c.

Among the pharmacologically active compounds which may be produced using the compounds of the present invention are 2-Phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole compounds which are useful as estrogenic agents. These compounds include those of the formulas IV and V, below:



wherein:

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R₁₁ is selected from H, OH or the C₁-C₁₂ esters (straight chain or branched) or C₁ - C₁₂ (straight chain or branched or cyclic) alkyl ethers thereof, or halogens; or halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

R¹², R⁹, and R¹⁰ are independently selected from H, OH or the C₁-C₁₂ esters (straight chain or branched) or C₁-C₁₂ alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C₁-C₆ alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH.

R¹³ is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen; and

Y, A, m, R³ and R⁴ are as defined herein.

The 2-Phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole compounds of this type are partial estrogen agonists and display high affinity for the estrogen receptor. Unlike many estrogens, however, these compounds do not cause increases in uterine wet weight. These compounds are antiestrogenic in the uterus and can completely antagonize the trophic effects of estrogen agonists in uterine tissue. These compounds are useful in treating or preventing in a mammal disease states or syndromes which are caused or associated with an estrogen deficiency.

These compounds have the ability to behave like estrogen agonists by lowering cholesterol and preventing bone loss. Therefore, these compounds are useful for treating many maladies including osteoporosis, prostatic hypertrophy, infertility, breast cancer, endometrial cancer, cardiovascular disease, contraception, Alzheimer's disease and melanoma. Additionally, these compounds can be used for hormone replacement therapy in post-menopausal women or in other estrogen deficiency states where estrogen supplementation would be beneficial.

The 2-Phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole compounds produced with the compounds of this invention may also be used in methods of treatment for bone loss, which may result from an imbalance in an individual's formation of new bone tissues and the resorption of older tissues, leading to a net loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal women, women who have undergone hysterectomy, those receiving or who have received

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extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone replacement can also be addressed using these compounds in individuals with bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis. In addition to those problems described above, these compounds can be used in treatments for osteoarthritis, Paget's disease, osteomalacia, osteomalacia, endometrial cancer, multiple myeloma and other forms of cancer having deleterious effects on bone tissues. Methods of treating the maladies listed herein are understood to comprise administering to an individual in need of such treatment a pharmaceutically effective amount of one or more of the compounds of this invention or a pharmaceutically acceptable salt thereof. This invention also includes pharmaceutical compositions utilizing one or more of the present compounds, and/or the pharmaceutically acceptable salts thereof, along with one or more pharmaceutically acceptable carriers, excipients, etc.

It is understood that the dosage, regimen and mode of administration of these 2-Phenyl-1-[4-(2-aminoethoxy)-benzyl]-indole compounds will vary according to the malady and the individual being treated and will be subject to the judgement of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

Effective administration of these compounds may be given at a dose of from about 0.1 mg/day to about 1,000 mg/day. Preferably, administration will be from about 50 mg/day to about 600 mg/day in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, parenterally (including intravenous, intraperitoneal and subcutaneous injections), and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

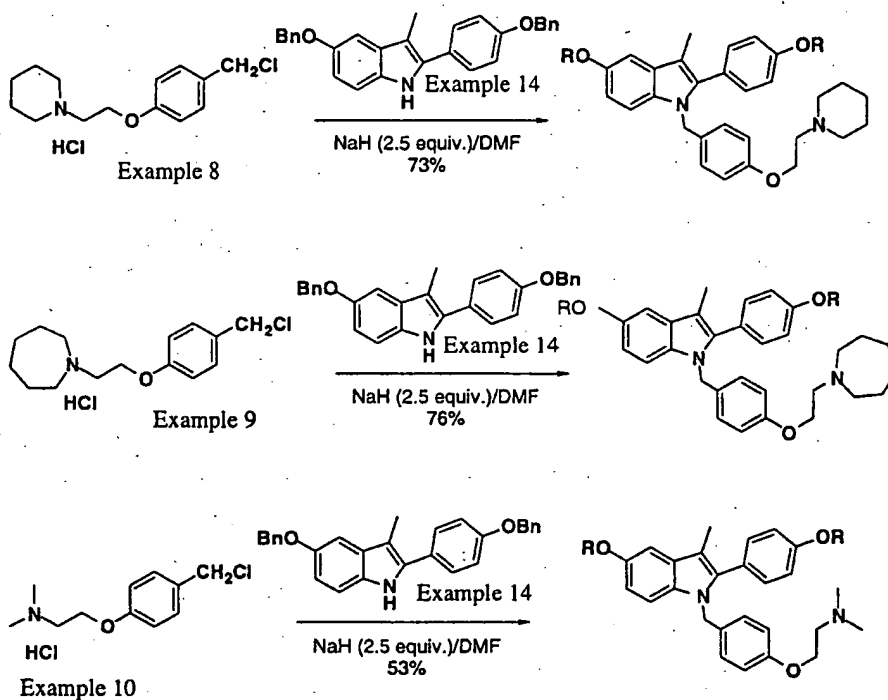
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Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, , xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may be utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

As shown in Scheme VI, compounds of this group can be synthesized by alkylation of the indole nitrogen with compounds of the present invention, as illustrated in Examples 11-13, below, utilizing (4-Chloromethyl-phenoxy)-ethyl-piperidin-1-yl hydrochloride of Example 8, (4-Chloromethyl-phenoxy)-ethyl- hexamethyleneimine -1-yl hydrochloride of Example 9 and (4-Chloromethyl-phenoxy)-ethyl-dimethylamino hydrochloride of Example 10, respectively. In addition to NaH, other bases may be used, including potassium t-butoxide or sodium t-butoxide.

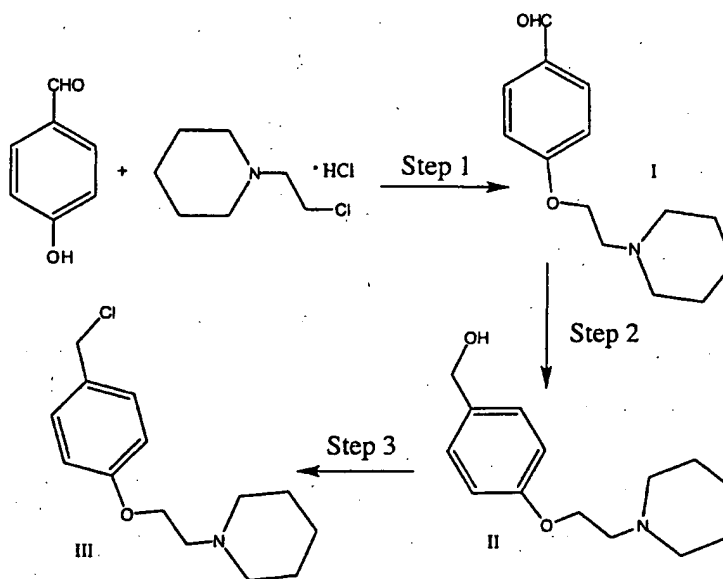
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Scheme VI

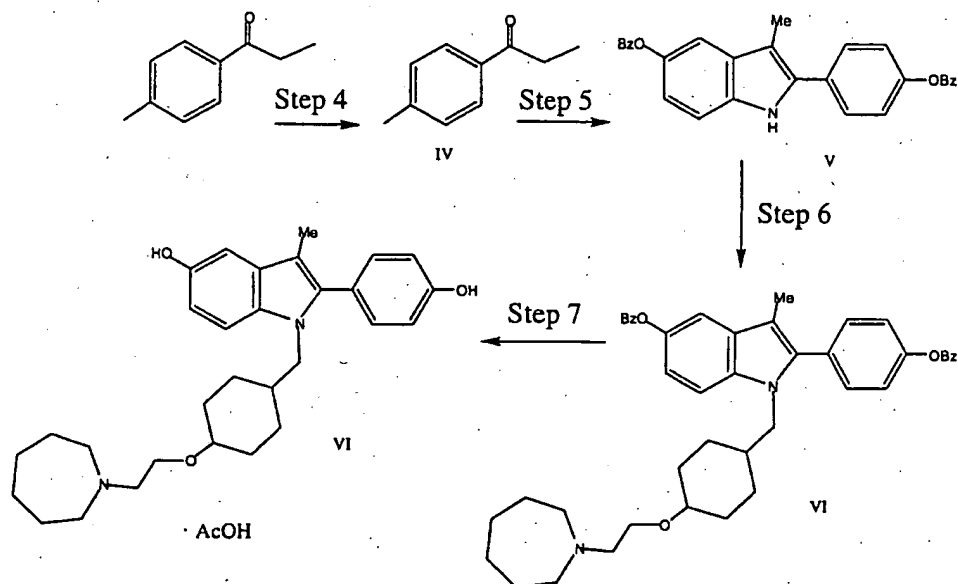
Schemes VII and VIII exemplify the synthesis of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol hydrochloride using intermediates of the present invention.

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Scheme VII

- 5 Scheme VII illustrates the alkylation of 4-hydroxybenzaldehyde with 2-(hexamethylamino)ethyl chloride hydrochloride, which can be accomplished in the presence of potassium carbonate to give corresponding aldehyde I (Step 1). When the reaction is complete the mixture may be clarified, mixed with toluene and washed with water. The toluene solution can then be concentrated and the resulting residue treated with isopropanol to give a solution of aldehyde I. The isopropanol solution of I may be treated to catalytic reduction, such as with Raney Nickel, to yield alcohol II (Step 2). Following reduction, the reaction mixture may be clarified and concentrated, with the resulting residue being dissolved in ethylene dichloride to give a solution containing alcohol II. This solution may be treated with thionyl chloride, followed by concentration. The resulting residue can then be treated with 1,2 dimethoxyethane to yield crystalline III (Step 3).
- 10
- 15

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Scheme VIII

In Scheme VIII, Step 4, 4-Benzyloxypropiophenone is brominated in acetic acid with bromine. When the reaction is complete the mixture can be quenched with water and the resulting precipitate is washed with dilute acetic acid, water and heptane. The resulting solid is dried to give IV, 4-benzyloxyaniline hydrochloride. In Step 5, a mixture of IV, N,N-diisopropylethylamine and toluene is heated under reflux with removal of water. When the reaction is complete the mixture may be cooled and diluted with methanol. The solids produced can be collected, washed with methanol and dried to give compound indole V. A mixture of compounds V and III can be mixed in Step 6 with sodium tert-butoxide in N,N-dimethylformamide and stirred until the reaction is complete. Then the mixture may be quenched with brine and extracted with toluene. The extracts are concentrated and the residue diluted with methanol. The resulting solids may be collected, dissolved in ethyl acetate, clarified, and diluted with methanol. The solids may be collected from this dilution and dried to give compound VI.

In a Step 7 (not shown) compound VI in a solution of ethanol can be hydrogenated with a Pd-charcoal catalyst. Following clarification, the hydrogenated material may be mixed with a small amount of ascorbic acid and treated with acetic acid. The resulting crystalline precipitate can then be collected, washed with ethanol and

dried to give the final product, 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol hydrochloride. The product may then be recrystallized from ethanol, optionally containing a small amount of ascorbic acid, preferably such as from about 0.5% by weight to about 3.0% by weight.

5

In the descriptions above, intermediates III through VI may be readily isolated as solids. All other intermediates may be more preferably used as solutions in organic solvents.

10

Schemes IX through XII exemplify the synthesis of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol utilizing intermediates of the present invention. Scheme IIa, described above, can be considered the first step of Scheme IX or a step prior thereto. In this step 4-hydroxybenzyl alcohol is treated with a desired aryl amino alkyl chloride to afford the corresponding alkoxy benzyl alcohol.

15

In the specific example of Scheme IIa, 4-hydroxybenzyl alcohol is treated with 1-(2-chloroethyl)-piperidine hydrochloride in the presence of K_2CO_3/Me_2CO to yield 4-(2-piperidinylethoxy)benzyl alcohol. Toluene and brine can be added to the resulting alcohol mixture to separate its phases. The toluene phase can then be washed successively with aqueous alkali and brine. The resulting batch can then be concentrated and ethylene dichloride added to form a solution of the intermediate, 4-(2-piperidinylethoxy)benzyl alcohol.

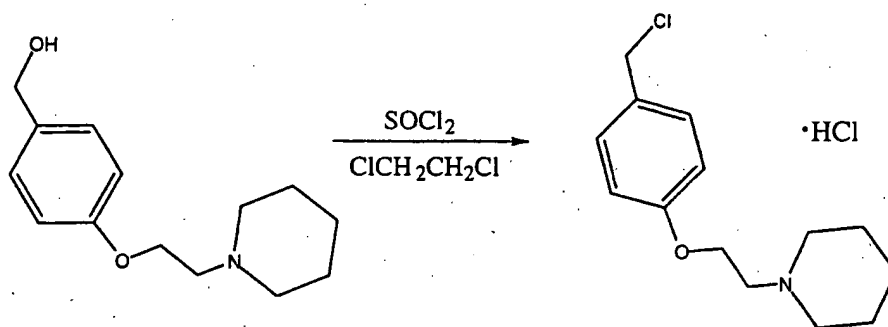
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The solution of 4-(2-piperidinylethoxy)benzyl alcohol in ethylene dichloride can be combined with thionyl chloride and heated until the reaction is complete. Upon cooling, the mixture can be concentrated, followed by addition of 1,2-dimethoxyethane and additional concentration. The precipitate can be collected and dried to yield intermediate 4-(2-piperidinylethoxy)benzylchloride hydrochloride, as shown in Scheme IX.

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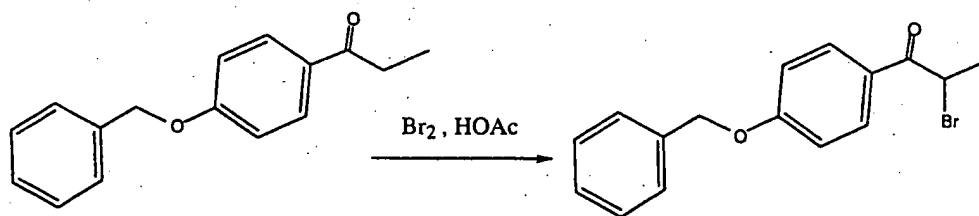
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Scheme IX

5

As shown in Scheme IX, a solution of 4-(2-piperidinyloxy)benzyl alcohol can be combined with ethylene dichloride and thionyl chloride and heated to create a reaction mixture. Upon cooling, the reaction mixture can be treated with 1,2-dimethoxyethane and concentrated, again. The resulting precipitate, 4-(2-piperidinyloxy)benzylchloride hydrochloride, can then be collected and dried.

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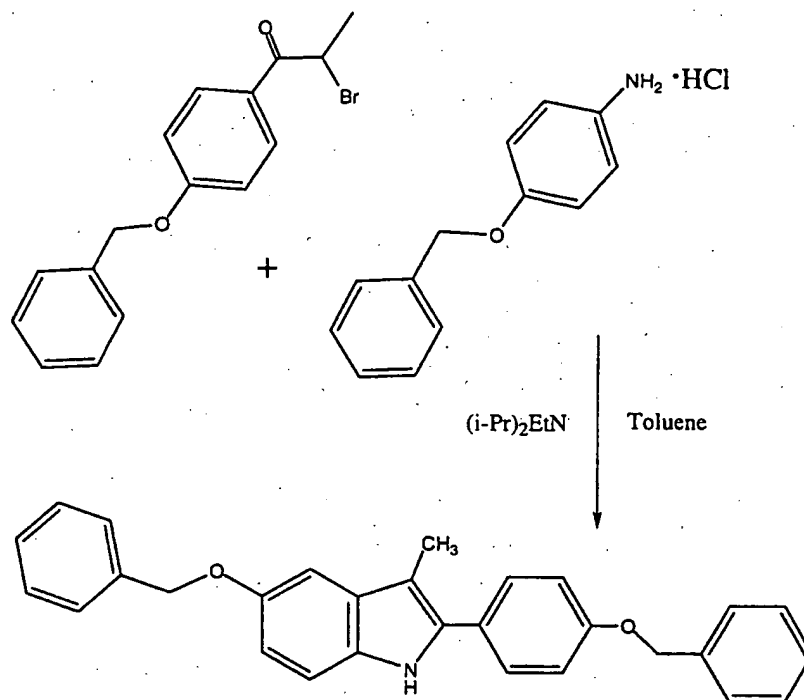
Scheme X

15

Scheme X depicts the bromination of 4-benzyloxypropiophenone in acetic acid with bromine to yield 4'-(benzyloxy)-2-bromopropiophenone. When this reaction is complete, the mixture can be quenched with water. The resulting precipitate can be collected, washed with dilute acetic acid, water and heptane, and dried.

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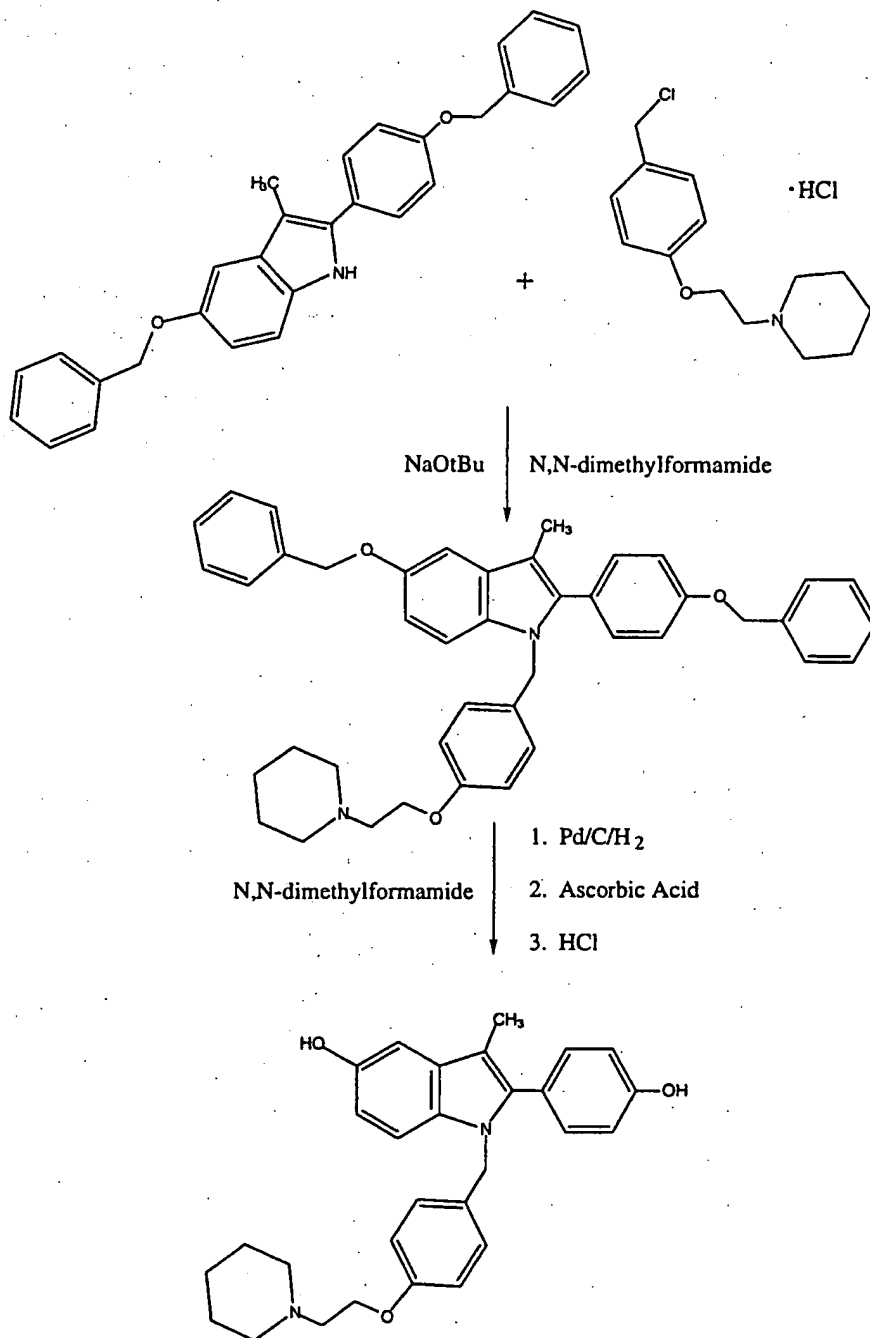
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Scheme XI

5 The 4'-(benzyloxy)-2-bromopropiophenone product of Scheme X can be heated with 4-benzyloxyaniline hydrochloride in the presence of N,N-diisopropylethylamine and toluene under reflux with the azeotropic removal of water, as shown in Scheme XI. When the reaction is complete, the mixture can be cooled and diluted with methanol. The resulting solids of 3-methyl-2-(4-benzyloxy)phenyl-5-benzyloxyindole can be collected, washed with methanol and dried.

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Scheme XII

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The 3-methyl-2-(4-benzyloxy)phenyl-5-benzyloxyindole product of Scheme XI can then be reacted with 4-(2-piperidinylethoxy)benzylchloride hydrochloride in the presence of sodium tert-butoxide in N,N-dimethylformamide. The resulting mixture can be quenched with brine and extracted with toluene. Following clarification, the extracts can be concentrated and diluted with methanol. The resulting solids of 5-Benzyloxy-2-(4-benzyloxyphenyl)-1-[4-(2-piperidin-1-yl-ethoxy)benzyl]-1H-indole can be collected, dissolved in ethyl acetate and diluted with methanol and dried. These solids can be dissolved in ethanol-tetrahydrofuran and hydrogenated using Pd-charcoal catalyst. The solution may then be clarified, optionally mixed with a small amount of ascorbic acid and then treated with aqueous HCl. The precipitate can then be collected, washed with ethanol-tetrahydrofuran and water and dried to yield the final product, of 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol.

EXAMPLE 11

15 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole

To a solution of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole (117.5 g, 0.28 mol, 1.0 eq.) in DMF (1.3 L), NaH (28.0 g, 60 % oil dispersion, 0.7 mol, 2.5 eq.) was added in portions at -5 / -8 °C over 1 h. The reaction mixture was stirred for 2 h. A solution of the chloride from Example 8 in THF (1.0 L) was added dropwise at -10 / 0 °C over 2 h. The reaction mixture was stirred at 25 °C overnight. TLC at this point showed no starting material, mostly product (EtOAc/hexane 1:5). The reaction mixture was diluted with water (6 L), extracted with EtOAc (2 x 3 L), and dried over Na₂SO₄. The solution was concentrated to 1 L, poured in MeOH (2.5 L), and stirred for 1 h. The precipitate was filtered and dried to give the title compound (129 g, 73 %).

1H NMR (CDCl₃/TMS): 7.64 - 6.63 (m, 21H), 5.12 (s, 2H), 5.09 (s, 2H), 5.07 (s, 2H), 4.07 (t, 2H, J = 6.06 Hz), 2.72 (t, 2H, J = 6.06 Hz), 2.48 (m, 4H), 2.24 (s, 3H), 1.62 - 1.24 (m, 6H).

EXAMPLE 12**5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-1-[4-(2-hexamethyleneimine-1-yl-ethoxy)-benzyl]-1H indole**

- 5 To a slurry of NaH (20.0 g, 60 % oil dispersion, 0.5 mol, 2.5 eq.) solution of 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole (84 g, 0.2 mol, 1.0 eq.) in DMF (100 mL) was added at 0 / + 10 °C over 1 h. The reaction mixture was stirred for 30 min. A solution of the chloride from Example 9 (67 g, 0.22 mol, 1.1 eq.) in DMF (200 mL) was added dropwise at 0 / + 10 °C over 2 h. The reaction mixture was
- 10 stirred at 25 °C for 2 h. TLC at this point showed no starting material, mostly product (EtOAc/hexane 1:5). The reaction mixture was diluted with water (1 L), extracted with EtOAc (3 x 1 L), and dried over MgSO₄. The solution was concentrated to 150 mL, poured in MeOH (750 mL), and stirred overnight. The precipitate was filtered and dried to give the title compound (99 g, 76 %).
- 15 ¹H NMR (CDCl₃/TMS): 7.48 - 6.74 (m, 21H), 5.13 (s, 2H), 5.11 (s, 2H), 5.09 (s, 2H), 4.00 (t, 2H, J = 6.24 Hz), 2.91 (t, 2H, J = 6.27 Hz), 2.75 (m, 4H), 2.24 (s, 3H), 1.71 - 1.52 (m, 8H)

EXAMPLE 13

20 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-1-[4-(2-dimethylaminoethoxy)-benzyl]-1H indole**

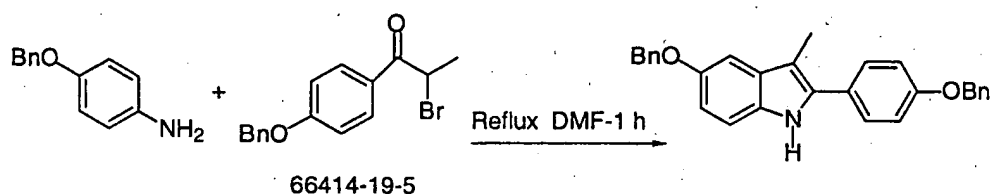
- To a slurry of NaH (1.1 g, 60 % oil dispersion, 0.05 mol, 2.5 eq.) solution of indole was added 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole (6.97 g,
- 25 0.017 mol, 1.0 eq.) in DMF (100 mL) at 0 / + 10 °C over 0.5 h. The reaction mixture was stirred for 30 min. A solution of the chloride from Example 10 (4.57 g, 0.018 mol, 1.1 eq.) was added portionwise at 0 / + 10 °C over 2 h. The reaction mixture was stirred at 25 °C for 0.5 h. TLC at this point showed no starting material, mostly product (EtOAc/hexane 1:5). The reaction mixture was diluted with water (200 mL),
- 30 extracted with EtOAc (3 x 200 mL), and dried over MgSO₄. The solution was concentrated to 150 mL, poured in MeOH (300 mL), and stirred overnight. The precipitate was filtered and dried to give the title compound 5.6 g (53 %).

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¹H NMR (CDCl₃/TMS): 7.50 - 6.66 (m, 21H), 5.13 (s, 2H), 5.11 (s, 2H), 5.09 (s, 2H), 3.99 (t, 2H, J = 5.76 Hz), 2.69 (t, 2H, J = 5.73 Hz), 2.31 (s, 6H), 2.42 (s, 3H)

EXAMPLE 14

5 **5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1H-indole**



A flask was charged with 4-benzyloxyaniline (45 g, 0.23 mol), 4'-benzyloxy-2-bromophenylpropiophenone (66414-19-5) (21g, 0.066 mol), and 50 mL DMF. The reaction was heated at reflux for 30 minutes and then cooled to rt and then partitioned between 250 mL EtOAc and 100 mL 1N HCl (aq). The EtOAc was washed with NaHCO₃ (aq) and brine, dried over MgSO₄. The solution was concentrated and the residue taken up in CH₂Cl₂ and hexanes added to precipitate out 25g of a crude solid. The solid was dissolved in CH₂Cl₂ and evaporated onto silica gel and chromatographed using CH₂Cl₂/Hexane (1:5) to yield 9.2 g of a tan solid (33%): Mpt = 150-152°C; ¹H NMR (DMSO) 10.88 (s, 1 H), 7.56 (d, 2 H, J = 8.8 Hz), 7.48 (d, 4 H, J = 7.9 Hz), 7.42-7.29 (m, 6 H), 7.21 (d, 1 H, J = 7.0 Hz), 7.13 (d, 2 H, J = 8.8 Hz), 7.08 (d, 1 H, J = 2.2 Hz), 6.94 (dd, 1 H, J = 8.8, 2.4 Hz), 5.16 (s, 2 H), 5.11 (s, 2 H), 2.33 (s, 3 H); IR (KBr) 3470, 2880, 2820, 1620 cm⁻¹; MS eI m/z 419.

EXAMPLE 15

25 **2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol**

A suspension of 10% Pd/C (1.1 g) in EtOH was treated with a solution of the title compound of Example 11 (2.2 g, 3.4 mmol) in THF/EtOH. Cyclohexadiene (6.0 mL, 63 mmol) was added and the reaction was stirred for 48 hours. The catalyst was filtered through Celite and the reaction mixture was concentrated and chromatographed on silica gel using a gradient elution of MeOH/CH₂Cl₂ (1:19 to 1:10) to yield 0.8 g of

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the product as a white solid. Mpt=109-113°C; CHN calc'd for $C_{29}H_{32}N_2O_3 + 0.5 H_2O$; 1H NMR 9.64 (s, 1 H), 8.67 (s, 1 H), 7.14 (d, 2 H, $J = 8.6$ Hz), 7.05 (d, 1 H, $J = 8.6$ Hz), 6.84 (d, 2 H, $J = 8.8$ Hz), 6.79 (d, 1 H, $J = 2.2$ Hz), 6.74 (s, 4 H), 6.56 (dd, 1 H, $J = 8.8, 2.4$ Hz), 5.09 (s, 2 H), 3.95-3.93 (m, 2 H), 2.60-2.51 (m, 2 H), 2.39-2.38 (m, 4 H), 2.09 (s, 3 H), 1.46-1.45 (m, 4 H), 1.35-1.34 (m, 2 H); IR (KBr) 3350 (br), 2920, 1620, 1510 cm^{-1} ; MS (EI) m/z 456.

In vitro estrogen receptor binding assay

10 Receptor preparation

CHO cells overexpressing the estrogen receptor were grown in 150 mm^2 dishes in DMEM + 10% dextran coated charcoal, stripped fetal bovine serum. The plates were washed twice with PBS and once with 10mM Tris-HCl, pH 7.4, 1mM EDTA. Cells were harvested by scraping the surface and then the cell suspension was placed on ice. Cells were disrupted with a hand-held motorized tissue grinder using two, 10-second bursts. The crude preparation was centrifuged at 12,000g for 20 minutes followed by a 60 minute spin at 100,000g to produce a ribosome free cytosol. The cytosol was then frozen and stored at -80°C. Protein concentration of the cytosol was estimated using the BCA assay with reference standard protein.

Binding assay conditions

The competition assay was performed in a 96-well plate (polystyrene*) which binds <2.0% of the total input [3H]-17 β -estradiol and each data point was gathered in triplicate. 100uG/100uL of the receptor preparation was aliquoted per well. A saturating dose of 2.5 nM [3H]17 β -estradiol + competitor (or buffer) in a 50 uL volume was added in the preliminary competition when 100x and 500x competitor were evaluated, only 0.8 nM [3H] 17 β -estradiol was used. The plate was incubated at room temperature for 2.5 h. At the end of this incubation period 150 uL of ice-cold dextran coated charcoal (5% activated charcoal coated with 0.05% 69K dextran) was added to each well and the plate was immediately centrifuged at 99g for 5 minutes at 4°C. 200 uL of the supernatant solution was then removed for scintillation counting. Samples were counted to 2% or 10 minutes, whichever occurs first. Because polystyrene

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absorbs a small amount of [³H]17₂-estradiol, wells containing radioactivity and cytosol, but not processed with charcoal were included to quantitate amounts of available isotope. Also, wells containing radioactivity but no cytosol were processed with charcoal to estimate unremovable DPM of [³H] 17₂-estradiol. Corning #25880-96, 96-well plates were used because they have proven to bind the least amount of estradiol.

Analysis of results

Counts per minute (CPM) of radioactivity were automatically converted to disintegrated per minute (DPM) by the Beckman LS 7500 Scintillation Counter using a set of quenched standards to generate a H# for each sample. To calculate the % of estradiol binding in the presence of 100 or fold 500 fold competitor the following formula was applied:

$$\frac{((\text{DPM sample} - \text{DPM not removed by charcoal}) / (\text{DPM estradiol} - \text{DPM not removed by charcoal})) \times 100\% = \% \text{ of estradiol binding}}$$

For the generation of IC₅₀ curves, % binding is plotted vs compound. IC₅₀'s are generated for compounds that show >30% competition at 500x competitor concentration. For a description of these methods, see Hulme, E.C., ed. 1992. Receptor-Ligand Interactions: A Practical Approach. IRL Press, New York. (see especially chapter 8). Reference in the tables below to the compound of Example 1 refer to the final product, 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol.

Estrogen Receptor Affinity (reported as RBA: 17₂-estradiol=100)

<u>Compound</u>	<u>RBA</u>
Raloxifene	200
Tamoxifen	1.8
Equilin	5.3
Example 15	400

Ishikawa Cell Alkaline Phosphatase Assay

Cell Maintenance and Treatment:

- 5 Ishikawa cells were maintained in DMEM/F12 (50%:50%) containing phenol red + 10% fetal bovine serum and the medium was supplemented with 2 mM Glutamax, 1% Pen/Strap and 1 mM sodium pyruvate. Five days prior to the beginning of each experiment (treatment of cells) the medium was changed to phenol red-free DMEM/F12 + 10% dextran coated charcoal stripped serum. On the day before
10 treatment, cells were harvested using 0.5% trypsin/EDTA and plated at a density of 5×10^4 cells/well in 96-well tissue culture plates. Test compounds were dosed at 10^{-6} , 10^{-7} and 10^{-8} M in addition to 10^{-6} M (compound) + 10^{-9} M 17 β -estradiol to evaluate the ability of the compounds to function as antiestrogens. Cells were treated for 48 h prior to assay. Each 96-well plate contained a 17 β -estradiol control. Sample
15 population for at each dose was n=8.

Alkaline Phosphatase Assay:

- At the end of 48h the media is aspirated and cells are washed three times with
20 phosphate buffered saline (PBS). 50 μ L of lysis buffer (0.1 M Tris-HCl, pH 9.8, 0.2% Triton X-100) is added to each well. Plates are placed at -80°C for a minimum of 15 minutes. Plates are thawed at 37°C followed by the addition of 150 μ L of 0.1 M Tris-HCl, pH 9.8, containing 4 mM para-nitrophenylphosphate (pNPP) to each well (final concentration, 3 mM pNPP). Absorbance and slope calculations were made
25 using the KineticCalc Application program (Bio-Tek Instruments, Inc., Winooski, VT). Results are expressed as the mean \pm S.D. of the rate of enzyme reaction (slope) averaged over the linear portion of the kinetic reaction curve (optical density readings every 5 minutes for 30 minutes absorbance reading). Results for compounds are summarized as percent of response related to 1 nM 17 β -estradiol. Various compounds
30 were assayed for estrogenic activity by the alkaline phosphatase method and corresponding ED50 values (95% C.I.) were calculated. The four listed in the following were used as as reference standards:

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17_-estradiol	0.03 nM	17_-estradiol	1.42 nM
estriol	0.13 nM	estrone	0.36 nM

- A description of these methods is described by Holinka, C.F., Hata, H., Kuramoto, H. and Gurside, E. (1986) Effects of steroid hormones and antisteroids on alkaline phosphatase activity in human endometrial cancer cells (Ishikawa Line). Cancer Research, 46:2771-2774, and by Littlefield, B.A., Gurside, E., Markiewicz, L., McKinley, B. and Hochberg, R.B. (1990) A simple and sensitive microtiter plate estrogen bioassay based on stimulation alkaline phosphatase in Ishikawa cells; Estrogen action of D5 adrenal steroids. Endocrinology, 6:2757-2762.

Ishikawa Alkaline Phosphatase Assay

<u>Compound</u>	<u>% Activation</u>
15 17_-estradiol	100% activity
tamoxifen	0% activity (45% with 1 nM 17_-estradiol)
raloxifene	5% activity (5% with 1 nM 17_-estradiol)
Example 15	1% activity (1% with 1 nM 17_-estradiol)

2X VIT ERE Transfection Assay

Cell Maintenance and Treatment

- Chinese Hamster Ovary cells (CHO) which had been stably transfected with the human estrogen receptor were maintained in DMEM + 10% fetal bovine serum (FBS). 48h prior to treatment the growth medium was replaced with DMEM lacking phenol red + 10% dextran coated charcoal stripped FBS (treatment medium). Cells were plated at a density of 5000 cells/well in 96-well plates containing 200 μ L of medium/well.

30 Calcium Phosphate Transfection

Reporter DNA (Promega plasmid pGL2 containing two tandem copies of the vitellogenin ERE in front of the minimal thymidine kinase promoter driving the

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luciferase gene) was combined with the B-galactosidase expression plasmid pCH110 (Pharmacia) and carrier DNA (pTZ18U) in the following ratio:

- 10uG of reporter DNA
- 5uG of pCH110DNA
- 5 5 uG of pTZ18U
- 20 uG of DNA/1 mL of transfection solution

- The DNA (20uG) was dissolved in 500 uL of 250 mM sterile CaCl₂ and added dropwise to 500 uL of 2 X HeBS (0.28 M NaCl, 50 mM HEPES, 1.5 mM Na₂HPO₄,
10 pH 7.05) and incubated at room temperature for 20 minutes. 20 uL of this mixture was added to each well of cells and remained on the cells for 16 h. At the end of this incubation the precipitate was removed, the cells were washed with media, fresh treatment media was replaced and the cells were treated with either vehicle, 1 nM 17_-estradiol, 1uM compound or 1 uM compound + 1 nM 17_-estradiol (tests for estrogen
15 antagonism). Each treatment condition was performed on 8 wells (n=8) which were incubated for 24 h prior to the luciferase assay.

Luciferase Assay

- 20 After 24h exposure to compounds, the media was removed and each well washed with 2 X with 125 uL of PBS lacking Mg⁺⁺ and Ca⁺⁺. After removing the PBS, 25 uL of Promega lysis buffer was added to each well and allowed to stand at room temperature for 15 min, followed by 15 min at -80°C and 15 min at 37°C. 20 uL of lysate was transferred to an opaque 96 well plate for luciferase activity evaluation
25 and the remaining lysate (5 uL) was used for the B-galactosidase activity evaluation (normalize transfection). The luciferan substrate (Promega) was added in 100 uL aliquots to each well automatically by the luminometer and the light produced (relative light units) was read 10 seconds after addition.

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Infection Luciferase Assay

<u>Compound</u>	<u>% Activation</u>
17_-estradiol	100% activity
5 estriol	38% activity
tamoxifen	0% activity (10% with 1 nM 17_-estradiol)
raloxifene	0% activity (0% with 1 nM 17_-estradiol)
Example 15	0% activity (0% with 1 nM 17_-estradiol)

10 B-Galactosidase Assay

To the remaining 5 uL of lysate 45 uL of PBS was added. Then 50 uL of Promega B-galactosidase 2X assay buffer was added, mixed well and incubated at 37°C for 1 hour. A plate containing a standard curve (0.1 to 1.5 milliunits in triplicate) was set up for each experimental run. The plates were analyzed on a Molecular Devices spectrophotometric plate reader at 410 nm. The optical densities for the unknown were converted to milliunits of activity by mathematical extrapolation from the standard curve.

20 Analysis of Results

The luciferase data was generated as relative light units (RLUs) accumulated during a 10 second measurement and automatically transferred to a JMP (SAS Inc) file where background RLUs were subtracted. The B-galactosidase values were automatically imported into the file and these values were divided into the RLUs to normalize the data. The mean and standard deviations were determined from a n=8 for each treatment. Compounds activity was compared to 17_-estradiol for each plate. Percentage of activity as compared to 17_-estradiol was calculated using the formula $\% = ((\text{Estradiol-control}) / (\text{compound value})) \times 100$. These techniques are described by Tzukerman, M.T., Esty, A., Santiso-Mere, D., Danielian, P., Parker, M.G., Stein, R.B., Pike, J.W. and McDonnell, D.P. (1994). Human estrogen receptor transactivational capacity was determined by both cellular and promoter context and mediated by two functionally distinct intramolecular regions (see Molecular Endocrinology, 8:21-30).

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Rat Uterotrophic/Antiuterotrophic Bioassay

The estrogenic and antiestrogenic properties of the compounds were determined in an immature rat uterotrophic assay (4 day) that (as described previously by L.J.Black and R.L.Goode, Life Sciences, 26, 1453 (1980)). Immature Sprague-Dawley rats (female, 18 days old) were tested in groups of six. The animals were treated by daily ip injection with 10 uG compound, 100 uG compound, (100 uG compound + 1 uG 17 β -estradiol) to check antiestrogenicity, and 1 uG 17 β -estradiol, with 50% DMSO/50% saline as the injection vehicle. On day 4 the animals were sacrificed by CO₂ asphyxiation and their uteri were removed and stripped of excess lipid, any fluid removed and the wet weight determined. A small section of one horn was submitted for histology and the remainder used to isolate total RNA in order to evaluate complement component 3 gene expression.

3 day Ovariectomized Rat Model

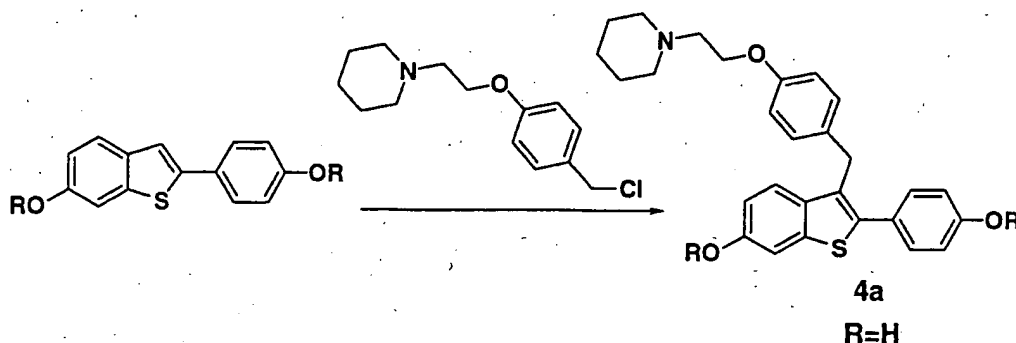
<u>Compound</u>	<u>10uG</u>	<u>100uG</u>	
Tamoxifen	69.6 mg	71.4 mg	
Raloxifen	47.5	43.2	
control = 42.7 mg		1 uG 17 β -estradiol = 98.2	

<u>Compound</u>	<u>10uG</u>	<u>100uG</u>	<u>100uG + 1uG 17β-estradiol</u>
Example 15	39.9 mg	27.4 mg	24.3 mg
control = 30.7 mg		1 uG 17 β -estradiol = 63.2	

The compound Raloxifen [2-(4-hydroxyphenyl)-6-hydroxybenzo[b]thien-3-yl][4-(1-piperidinyl)ethoxy]phenyl-methanone hydrochloride is representative of a class of compounds known to be selective estrogen receptor modulators, possessing estrogen agonist-like actions on bone tissues and serum lipids while exhibiting estrogen antagonism in uterine and breast tissues. Palkowitz et al. suggest in J. Med. Chem 1997, 40, 1407 active analogs of Raloxifen which may also be produced utilizing the compounds of this invention. For instance, their disclosed compound 4a, [2-(4-

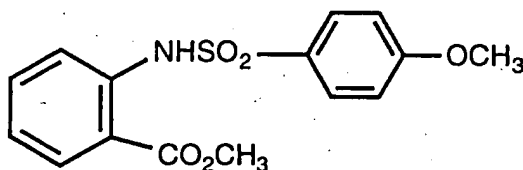
- 48 -

hydroxyphenyl)-6-hydroxybenzo[*b*]thien-3-yl][4-(1-piperidinyl)ethoxy] phenyl-methane hydrochloride can be produced by the general reaction scheme below.



EXAMPLE 16

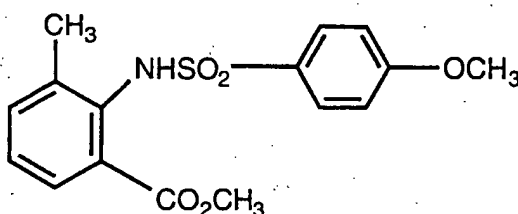
5 2-(4-Methoxy-benzenesulfonylamino)-benzoic acid methyl ester



To a solution of 2.00g (0.013mol) of methyl anthranilate dissolved in 20mL of chloroform was added 3.2mL (0.039mol) of pyridine followed by 2.733g (0.013mol) of p-methoxybenzenesulfonyl chloride. The reaction mixture was stirred at room temperature for 5h and then washed with 3N HCl and water. The organics were then dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting white solid was washed with ether and dried in vacuo to provide 3.7g (87%) of the desired sulfonamide. CI Mass Spec: 322 (M+H).

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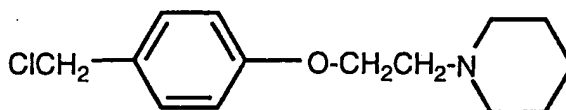
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EXAMPLE 17**2-(4-Methoxy-benzenesulfonylamino)-3-methyl-benzoic acid methyl ester**

5

In the same manner as described in Example 16, 6.24g (0.038mol) of methyl-3-methyl-anthranilate provided 6.21g (49%) of the desired sulfonamide as a white solid. Electrospray Mass Spec 336.2 (M+H).

10

EXAMPLE 18**4-(2-Piperidin-1-yl-ethoxy)-benzyl chloride**

15

To a stirred solution of 4-hydroxy benzaldehyde (12.2 gm, 0.1 mol) and K₂CO₃ (25 gm, excess) in N,N-dimethylformamide (250 ml) was added 1-(2-chloroethyl)piperidine monohydrochloride (20.0 gm, 1.08 mol). The reaction mixture was heated to 80°C for 24 hrs and cooled to room temperature. The reaction mixture was quenched with ice cold water and extracted with chloroform. The organics were washed with water, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The residue was dissolved in methanol and sodium borohydride (10 gms, excess) was slowly added at 0°C. The reaction mixture was stirred at room temperature for 2h and then quenched with water. The alcohol was extracted with chloroform, the organics were washed well with water, dried over Na₂SO₄, filtered and concentrated in vacuo.

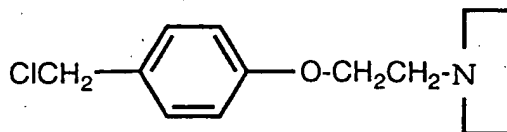
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25

The crude alcohol thus obtained was dissolved in THF (200 ml) and HCl gas was passed through for 30 minutes at 0°C. To the suspension of hydrochloride thus

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obtained, thionyl chloride (30 ml, excess) was slowly added. The reaction mixture was refluxed for thirty minutes and cooled to room temperature. The reaction mixture was then concentrated to dryness and triturated with anhydrous ether. The precipitated solid was filtered and dried under vacuum at room temperature to give 25g (86%) of the product as a white solid. m.p. 145 - 148_C. Electrospray Mass Spec: 256 (M+H).

EXAMPLE 19**4-(2-N,N-Diethyl-ethoxy)-benzyl chloride**

10

To a stirred solution of 4-hydroxy benzaldehyde (12.2 gm, 0.1 mol) and K_2CO_3 (25 gm, excess) in N,N-dimethylformamide (250 ml) was added 2-diethyl-aminoethyl chloride monohydrochloride (20.0 gm, 1.2 mol). The reaction mixture was heated at 80_C for 24 hrs and cooled to room temperature. The reaction mixture was quenched with ice cold water and extracted with chloroform. The organics were washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in methanol and sodium borohydride (10 gms, excess) was slowly added at 0_C. The reaction mixture was stirred at room temperature for 2h and then quenched with water. The alcohol was extracted with chloroform, washed well with water, dried, filtered and concentrated in vacuo.

20

The crude alcohol thus obtained was dissolved in THF (200 ml) and HCl gas was passed through for 30 minutes at 0_C. To the suspension of hydrochloride thus obtained, thionyl chloride (30 ml, excess) was slowly added. The reaction mixture was refluxed for thirty minutes and cooled to room temperature. The reaction mixture was then concentrated to dryness and triturated with anhydrous ether. The precipitated solid was filtered and dried under vacuum at room temperature to give 18g (65%) of the product as a white solid, m.p. 76-79_C. Electrospray Mass Spec: 244 (M+H).

25

30

EXAMPLE 20**N-Hydroxy-2-[[[(4-methoxyphenyl)sulfonyl][[4-[2-(1-piperidinyl)ethoxy]phenyl]methyl]amino]-3-methylbenzamide**

5 To a solution of 1.00 g (2.985 mmol) of 2-(4-methoxy-benzene-sulfonylamino)-3-methyl-benzoic acid methyl ester in 5 ml of DMF was added 0.952 g (3.284 mmol) of 4-(2-piperidin-1-yl-ethoxy)benzyl chloride and 1.65 g (11.9 mmol) of potassium carbonate. The reaction mixture was then stirred at room temperature for 18 h, diluted with water and extracted with ether. The organics were then extracted
10 with 6 N HCl solution and the aqueous acid layer was then basified with 6 N NaOH solution and then extracted with ether. The resulting ether layer was dried over sodium sulfate, filtered and concentrated in vacuo to provide 0.965 g of the piperidine-ester as a colorless oil. Electrospray Mass Spec: 553.5 (M+H)⁺.

15 To a solution of 0.889 g (1.611 mmol) of piperidine ester in 7 ml of THF was added 0.203 g lithium hydroxide monohydrate. The resulting mixture was heated to reflux for 15 h, and then concentrated in vacuo to a residue. The residue was diluted with water, neutralized with 5% HCl solution and extracted with dichloromethane. The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo to provide
20 0.872 g of the carboxylic acid as a white foam. Electrospray Mass Spec: 539.2 (M+H)⁺.

To a solution of 0.814 g (1.513 mmol) of the carboxylic acid in 10 ml of DMF was added 0.245 g (1.82 mmol) of HOBt and 0.386 g (2.01 mmol) of EDC. The
25 reaction was then stirred for 1 h at room temperature and 0.46 ml (7.57 mmol) of a 50% solution of hydroxylamine in water was added. The reaction was stirred overnight and then concentrated in vacuo to a residue. The residue was diluted with EtOAc, washed with water and sodium bicarbonate solution, dried over Na₂SO₄, filtered and concentrated in vacuo to a residue. The residue was dissolved in 5 ml of
30 dichloromethane and 0.69 ml of a 1 N solution of HCl in ether was added. After 1 h the reaction was diluted with ether and the resulting solid was filtered and dried in vacuo to give 0.179 g of the hydroxamate-amine salt as a white solid. Electrospray Mass Spec: 554.5 (M+H)⁺.

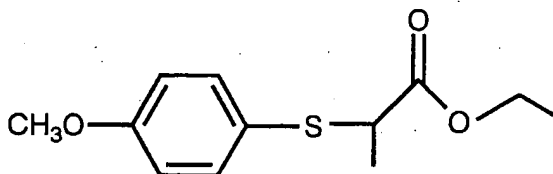
EXAMPLE 21**2-[[4-(2-Diethylamino-ethoxy)-benzyl]-(4-methoxy-benzenesulfonyl)-aminol]-N-hydroxy-3-methyl-benzamide**

5 To a solution of 1.0 g (2.653 mmol) of 2-(4-methoxybenzene-sulfonylamino)-3-methylbenzoic acid methyl ester in 10 ml of DMF was added 0.811 g (2.918 mmol) of 4-(2-N,N-diethyl-ethoxy)-benzyl chloride and 1.5 g (10.9 mmol) of potassium carbonate. The reaction mixture was then stirred at room temperature for 18 h, diluted with water and extracted with ether. The organics were then extracted with 6 N HCl
10 solution and the aqueous acid layer was then basified with 6 N NaOH solution and then extracted with ether. The resulting ether layer was dried over sodium sulfate, filtered and concentrated in vacuo to provide 0.575 g (37%) of the N,N-diethylamino-ester as a tan foam. Electrospray Mass Spec: 583.1 (M+H)⁺.

15 To a solution of 0.539 g (0.926 mmol) of the N,N-diethylamino-ester in dichloromethane was added 2 mL of trifluoroacetic acid. The reaction was stirred at room temperature for 2 h and then concentrated in vacuo to a residue. The residue was triturated with ether and the resulting solid was collected by filtration and dried in vacuo to give 0.369 g of the carboxylic acid as a white solid. Electrospray Mass Spec: 525.2
20 (M-H)⁻.

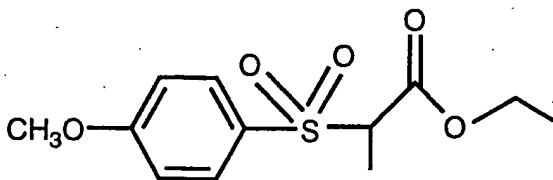
To a solution of 0.328 g (0.513 mmol) the carboxylic acid in 6.5 ml of dichloromethane was added 0.12 ml of DMF followed by 0.77 ml of 2.0 M oxalyl chloride in CH₂Cl₂ and the reaction mixture was stirred at room temperature for 1 h.

25 In a separate flask was added at 0°C to a mixture of 0.47 mL (7.7 mmol) of a 50% solution of hydroxylamine in water 8 ml of THF and 1.7 ml of water. After this mixture had stirred for 15 minutes at 0°C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature with
30 stirring overnight. The reaction mixture was then acidified to pH 3 with 10% HCl and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo to a residue. The residue is triturated with ether to provide 0.194 g of the hydroxamate-amine salt as a white solid. Electrospray Mass Spec: 542.3 (M+H)⁺.

EXAMPLE 22**2-(4-Methoxy-phenylsulfanyl)-propionic acid ethyl ester**

5 To a stirred solution of 4-methoxybenzenethiol (2.5 gm, 14 mmol) and anhydrous K_2CO_3 (4.0 gm, excess) in dry acetone (100 ml), ethyl 2-bromo-propionate (3.0 gm, 16 mmol) was added in a round bottom flask and the reaction mixture was heated at reflux for 8 hours with good stirring. At the end, reaction was allowed to cool, filtered and the reaction mixture was concentrated to a residue. The residue was
10 extracted with chloroform and washed with H_2O and the organic layer dried over $MgSO_4$, filtered and concentrated to afford 2-(4-methoxy-phenylsulfanyl)-propionic acid ethyl ester as a light yellow oil. Yield 3.6 gms (94%).

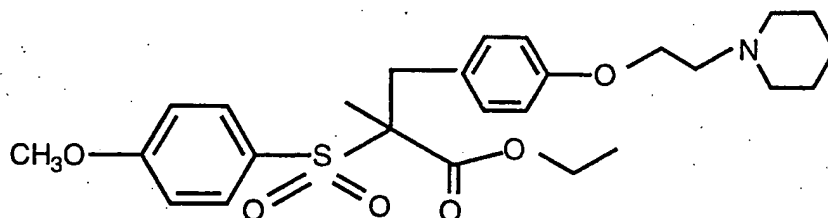
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EXAMPLE 23**2-(4-Methoxy-benzenesulfonyl)-propionic acid ethyl ester**

20 To a stirred solution of 12.0 gm (50 mmol) of 2-(4-methoxy-phenylsulfanyl)-propionic acid ethyl ester in 300 ml of methylene chloride at $0^\circ C$ was slowly added at a rate to control the exotherm. The reaction mixture was stirred at room temperature for 2 hours and diluted with 600 ml of hexanes. The reaction mixture was filtered and the filtrate stirred with 500 ml of a saturated Na_2SO_3 solution for 3 hours. The organic
25 layer was separated, washed well with water, dried and evaporated in vacuo to give 12 gm of a semi-solid.

EXAMPLE 24**2-(4-Methoxy-benzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]propionic acid ethyl ester**

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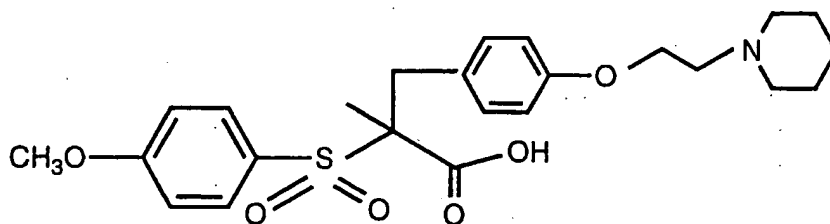


To a stirred mixture of 2.7 g (10 mmol) of 2-(4-methoxy-benzenesulfonyl)propionic acid ethyl ester, 3.03 gm (10 mmol) 4-(2-piperidin-1-yl-ethoxy)benzyl chloride, 10 gm of K₂CO₃ and 500 mg of 18-crown-6 in 250 ml of acetone was refluxed for 16 hours. At the end, the reaction mixture was filtered and the acetone layer was concentrated to a residue. The residue was extracted with chloroform, washed well with water, dried over anhydrous MgSO₄, filtered and concentrated to a residue. The residue obtained was purified by silica-gel column chromatography by eluting with 50% ethyl acetate-hexanes to afford 4.8 gm (92%) of the desired product as an oil. MS: 490(M+H)⁺.

15

EXAMPLE 25**2-(4-Methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidinyl-1-yl-ethoxy)-phenyl]-propionic acid**

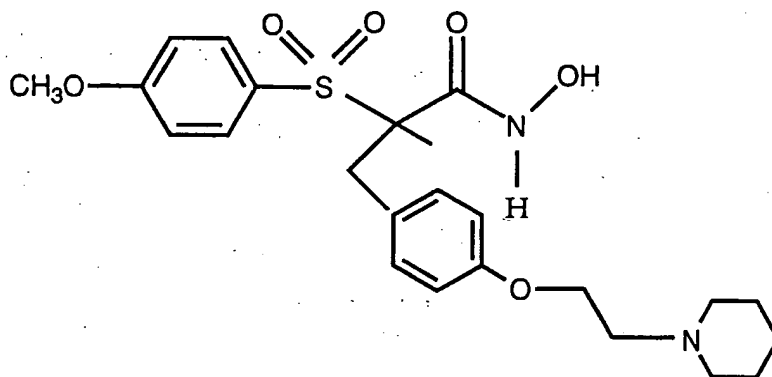
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To a stirred solution of 2-(4-methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-yl-ethoxy)phenyl]propionic acid ethyl ester (4.9 gm, 10 mmol) in methyl alcohol was added 10 N NaOH (20 ml, excess). The reaction mixture was stirred at room temperature for 48 hours. At the end, the reaction mixture was concentrated and carefully neutralized with dilute HCl. The residue obtained was extracted with chloroform, washed well with water, dried and concentrated. The product obtained was purified by silica gel column chromatography by eluting with ethyl acetate:methanol (95:5) to afford the product of the example as colorless crystals, m.p. 106°C; MS: 462.5 (M+H)⁺. Yield 4.1 gm, 88-1.

10

EXAMPLE 26**2-(4-Methoxybenzenesulfonyl)-2-methyl-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-propionamide**

To a stirred solution of 2-(4-methoxy-phenylsulfonyl)-2-methyl-3-phenyl-[4-(2-piperidin-1-yl-ethoxy)]propionic acid (2.3 g, 5 mmol) of DMF (2 drops) in CH₂Cl₂ (100 ml) at 0°C, oxalyl chloride (1.2 gm, 10 mmol) was added in a dropwise manner. After the addition, the reaction mixture was stirred at room temperature for 1 hour. Simultaneously, in a separate flask a mixture of hydroxylamine hydrochloride (3.4 gm, 50 mmol) of triethylamine (10.1 gm, 100 mmol) was stirred in THF:water (5:1, 50 ml) at 0°C for 1 hour. At the end of 1 hour, the oxalyl chloride reaction mixture was concentrated and the pale yellow residue was dissolved in 10 ml of CH₂Cl₂ and added slowly to the hydroxylamine at 0°C. The reaction mixture was stirred at room temperature for 24 hours and concentrated. The residue obtained was extracted with chloroform and washed well with water. The product obtained was purified by silica

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gel column chromatography and eluted with ethyl acetate. The product of the example was isolated as a colorless solid. mp 98°C; Yield, 48%; MS: 477 (M+H)⁺; ¹H NMR (300 MHz, CDCl₃): δ 1.2 (s, 3H), 3.5-1.5 (m, 16H), 3.9 (s, 3H), 4.4 (m, 1H); 6.5-7.8 (m, 8H); 10.8 (bs, 1H).

5

The subject compounds of the present invention were tested for biological activity according to the following procedures.

In Vitro Gelatinase Assay

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The assay is based on the cleavage of the thiopeptide substrate ((Ac-Pro-Leu-Gly(2 mercapto-4 methyl-pentanoyl)-Leu-Gly-OEt), Bachem Bioscience) by the enzyme, gelatinase, releasing the substrate product which reacts colorimetrically with DTNB ((5,5'-dithio-bis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM CaCl₂) before use. The stock of human neutrophil gelatinase B is diluted with assay buffer (50 mM HEPES pH 7.5, 5 mM CaCl₂, 0.02% Brij) to a final concentration of 0.15 nM. The assay buffer, enzyme, DTNB/substrate (500 μ M final concentration) and vehicle or inhibitor are added to a 96 well plate (total reaction volume of 200 μ l) and the increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader. The increase in OD₄₀₅ is plotted and the slope of the line is calculated which represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm$ sem) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and IC₅₀ values with 95% CI are estimated using linear regression (IPRED, HTB).

References: Weingarten, H and Feder, J., Spectrophotometric assay for vertebrate collagenase, Anal. Biochem. 147, 437-440 (1985).

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In Vitro Collagenase Assay

The assay is based on the cleavage of a peptide substrate ((Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMa)-NH₂), Peptide International, Inc.) by collagenase releasing the fluorescent NMa group which is quantitated on the fluorometer. Dnp quenches the NMa fluorescence in the intact substrate. The assay is run in HCBC assay buffer (50 mM HEPES, pH 7.0, 5 mM Ca⁺², 0.02% Brij, 0.5% Cysteine), with human recombinant fibroblast collagenase (truncated, mw=18,828, WAR, Radnor). Substrate is dissolved in methanol and stored frozen in 1 mM aliquots. Collagenase is stored frozen in buffer in 25 μ M aliquots. For the assay, substrate is dissolved in HCBC buffer to a final concentration of 10 μ M and collagenase to a final concentration of 5 nM. Compounds are dissolved in methanol, DMSO, or HCBC. The methanol and DMSO are diluted in HCBC to < 1.0%. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and IC₅₀ values with 95% CI are estimated using linear regression (IPRED, HTB).
References: Bickett, D. M. et al., A high throughput fluorogenic substrate for interstitial collagenase (MMP-1) and gelatinase (MMP-9), Anal. Biochem. 212,58-64 (1993).

25

Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 μ L TACE (Immunex, final concentration 1 μ g/mL), 70 μ L Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 μ L of test compound solution in DMSO (final concentration 1 μ M, DMSO concentration <1%) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 μ M) to each well and then shaking on a shaker for 5 sec. The reaction is read (excitation 340 nm, emission 420

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nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

The results obtained following these standard experimental test procedures are presented in the following table.

Example	IC 50 (nM or % inhibition at 1 micromolar)			
	MMP 1	MMP 9	MMP 13	TACE
26	238.6	8.9	1.4	41.00%

Procedures for Measuring MMP-1, MMP-9, and MMP-13 Inhibition

These assays are based on the cleavage of a thiopeptide substrates such as Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt by the matrix metalloproteinases MMP-1, MMP-13 (collagenases) or MMP-9 (gelatinase), which results in the release of a substrate product that reacts colorimetrically with DTNB (5,5'-dithiobis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in the dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM $CaCl_2$) before use. The stock of enzyme is diluted with assay buffer (50 mM HEPES, pH 7.5, 5 mM $CaCl_2$, 0.02% Brij) to the desired final concentration. The assay buffer, enzyme, vehicle or inhibitor, and DTNB/substrate are added in this order to a 96 well plate (total reaction volume of 200 μ l) and the increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader and the increase in color over time is plotted as a linear line.

30

Alternatively, a fluorescent peptide substrate is used. In this assay, the peptide substrate contains a fluorescent group and a quenching group. Upon cleavage of the substrate by an MMP, the fluorescence that is generated is quantitated on the

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fluorescence plate reader. The assay is run in HCBC assay buffer (50mM HEPES, pH 7.0, 5 mM Ca^{+2} , 0.02% Brij, 0.5% Cysteine), with human recombinant MMP-1, MMP-9, or MMP-13. The substrate is dissolved in methanol and stored frozen in 1 mM aliquots. For the assay, substrate and enzymes are diluted in HCBC buffer to the
5 desired concentrations. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line.

10 For either the thiopeptide or fluorescent peptide assays, the slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($\bar{x} \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple
15 doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

In vivo MMP Inhibition

A 2 cm piece of dialysis tubing (molecular weight cut-off 12-14,000, 10 mm
20 flat width) containing matrix metalloproteinase enzyme (stromelysin, collagenase or gelatinase in 0.5 mL of buffer) is implanted either ip or sc (in the back) of a rat (Sprague-Dawley, 150-200g) or mouse (CD-1, 25-50g) under anesthesia. Drugs are administered PO, IP, SC or IV through a canula in the jugular vein. Drugs are administered in a dose volume of 0.1 to 0.25 mL/animal. Contents of the dialysis
25 tubing is collected and enzyme activity assayed.

Enzyme reaction rates for each dialysis tube are calculated. Tubes from at least 3 different animals are used to calculate the mean \pm sem. Statistical significance ($p < 0.05$) of vehicle-treated animals versus drug-treated animals is determined by
30 analysis of variance. (*Agents and Actions* 21: 331, 1987).

Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 μ L TACE (Immunex, final concentration 1 μ g/mL), 70 μ L Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 μ L of test compound solution in DMSO (final concentration 1 μ M, DMSO concentration <1%) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 μ M) to each well and then shaking on a shaker for 5 sec.

The reaction is read (excitation 340 nm, emission 420 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate.

The linearity of the reaction rate is confirmed ($r^2 > 0.85$). The mean ($x \pm \text{sem}$) of the control rate is calculated and compared for statistical significance ($p < 0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and IC₅₀ values with 95% CI are estimated using linear regression.

Results of the above in-vitro and in-vivo matrix metalloproteinase inhibition and TACE inhibition pharmacological assays are given in Table I below.

Table I. Inhibition of MMP and TACE

Example	MMP-1 ¹	MMP-9 ¹	MMP-13 ¹	in-vivo	
				MMP ²	TACE ¹
20	176	6.9	56		277
21	96	2.3	8.8		215

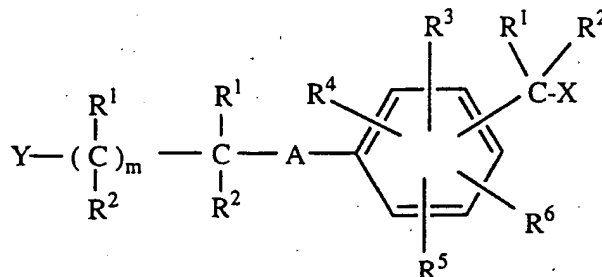
1. IC₅₀ nM or % inhibition at 1 μ M concentration

2. % inhibition vs. MMP-9(dose, mg/kg), ip = intraperitoneal, po = oral

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What is Claimed:

1. A compound of the formula:

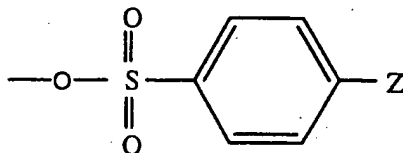


(I)

- 5 wherein:

R^1 and R^2 are, independently, selected from H; C_1 - C_{12} alkyl or C_1 - C_6 perfluorinated alkyl;

- 10 X selected from halogen, $-O-SO_2-CH_3$, $-O-SO_2-CF_3$, or a moiety of the structure:



Z is $-NO_2$, halogen, $-CH_3$ or $-CF_3$;

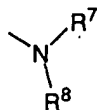
A is selected from $-O-$ or $-S-$, $-SO-$ or $-SO_2-$;

m is an integer from 0 to 3;

- 15 R^3 , R^4 , R^5 , and R^6 are independently selected from H, halogen, $-NO_2$, alkyl, alkoxy, C_1 - C_6 perfluorinated alkyl, OH or the C_1 - C_4 esters or alkyl ethers thereof, $-CN$, $-O-R^1$, $-O-Ar$, $-S-R^1$, $-S-Ar$, $-SO-R^1$, $-SO-Ar$, $-SO_2-R^1$, $-SO_2-Ar$, $-CO-R^1$, $-CO-Ar$, $-CO_2-R^1$, or $-CO_2-Ar$; and

Y is selected from:

- 20 a) the moiety:



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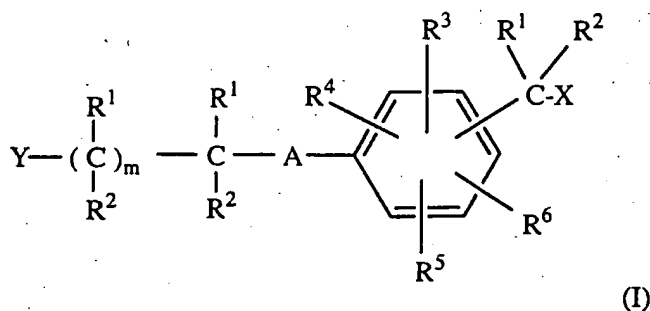
wherein R7 and R8 are independently selected from the group of H, C₁-C₆ alkyl, or phenyl;

- b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;
- c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;
- d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂; or

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- e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, and -S(O)_n-, wherein n is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;
- 10 and the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:

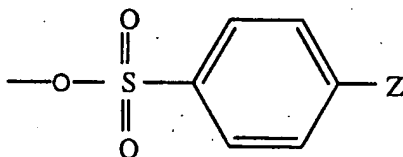


wherein:

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R¹ and R² are, independently, selected from H; C₁-C₁₂ alkyl or C₁-C₆ perfluorinated alkyl;

X is halogen, -O-SO₂-CH₃, -O-SO₂-CF₃, or a moiety of the structure:



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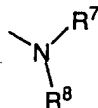
Z is -NO₂, halogen, -CH₃ or -CF₃;

A is selected from -O- or -S-, -SO- or -SO₂-;

m is an integer from 0 to 3; and

Y is selected from:

a) the moiety:



5 wherein R7 and R8 are independently selected from the group of H, C1-C6 alkyl, or phenyl;

b) a group selected from thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, isoxazole, or oxathiolane, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C1-C4 alkyl, trihalomethyl, C1-C4 alkoxy, trihalomethoxy, C1-C4 acyloxy, C1-C4 alkylthio, C1-C4 alkylsulfinyl, C1-C4 alkylsulfonyl, hydroxy (C1-C4)alkyl, phenyl optionally substituted with 1-3 (C1-C4)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C1-C4 alkylamino, C1-C4 dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

c) a group selected from pyridine, pyrazine, pyrimidine, pyridazine, piperidine, morpholine and pyran, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C1-C4 alkyl, trihalomethyl, C1-C4 alkoxy, trihalomethoxy, C1-C4 acyloxy, C1-C4 alkylthio, C1-C4 alkylsulfinyl, C1-C4 alkylsulfonyl, hydroxy (C1-C4)alkyl, phenyl optionally substituted with 1-3 (C1-C4)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C1-C4 alkylamino, C1-C4 dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

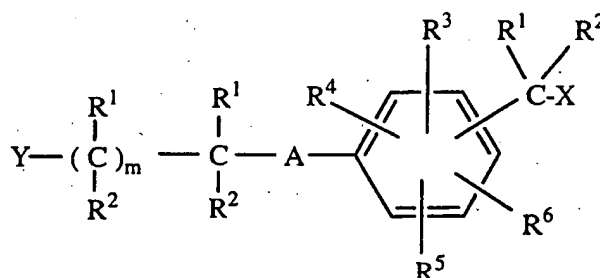
d) a group selected from azepine, diazepine, oxazepine, thiazepine, oxapin and thiepin, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C1-C4 alkyl, trihalomethyl, C1-C4 alkoxy, trihalomethoxy, C1-C4 acyloxy, C1-C4 alkylthio, C1-C4 alkylsulfinyl, C1-C4 alkylsulfonyl, hydroxy (C1-C4)alkyl, phenyl optionally substituted with 1-3 (C1-C4)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C1-C4 alkylamino, C1-C4 dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂; or

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- e) a bicyclic heterocycle selected from the group of benzofuran, isobenzofuran, benzothiophene, indole, isoindole, indolizine, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, and cinnoline, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;

and the pharmaceutically acceptable salts thereof.

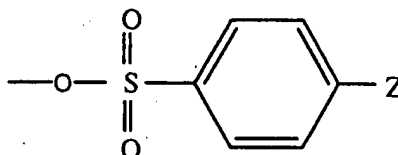
3. A compound of Claim 1 of the formula:



wherein:

R¹ and R² are, independently, selected from H, preferably C₁-C₆ alkyl or C₁-C₆ perfluorinated alkyl;

X is halogen, -O-SO₂-CH₃, -O-SO₂-CF₃, or a moiety of the structure:



Z is selected from -NO₂, halogen, -CH₃ or -CF₃;

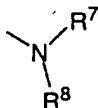
A is selected from -O- or -S-, -SO- or -SO₂-;

m is an integer from 0 to 3; and

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Y is selected from:

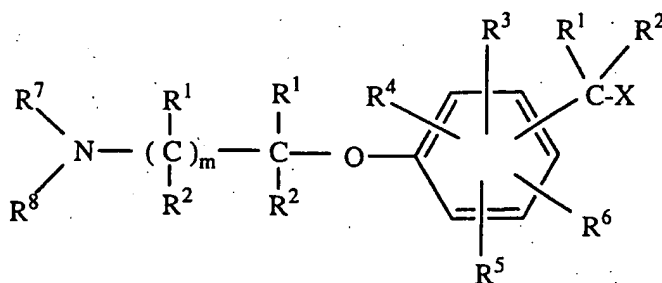
a) the moiety:



5 wherein R7 and R8 are independently selected from the group of H, C₁-C₆ alkyl, or phenyl; or

b) a group selected from thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, pyridine, pyrazine, pyrimidine, pyridazine, piperidine, indole or benzofuran, the group being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, phenyl optionally substituted with 1-3 (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR¹, -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂R¹, -NHCOR¹, -NO₂;
15 and the pharmaceutically acceptable salts thereof.

4. A compound of Claim 1 of the formula:



20 wherein:

R¹ and R² are, independently, selected from H, C₁-C₆ alkyl or C₁-C₆ perfluorinated alkyl;

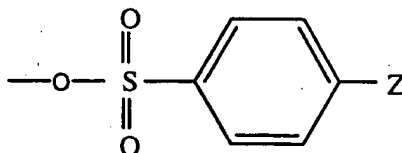
R³, R⁴, R⁵, and R⁶ are independently selected from H, OH or the C₁-C₄ esters or alkyl ethers thereof, halogen, -CN, C₁-C₆ alkyl, or trifluoromethyl,

25 m is an integer from 0 to 3;

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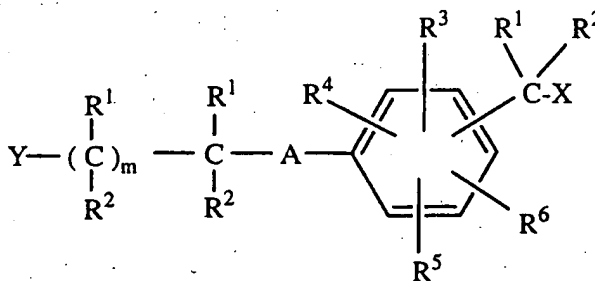
R^7 and R^8 are selected independently from H, C₁-C₆ alkyl, or combined by -
 (CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being
 optionally substituted by up to three substituents selected from the group of hydrogen,
 hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄
 5 alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -
 CN, -CONH(C₁-C₄), -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-
 C₄), -NHCO(C₁-C₄), and -NO₃; and

X is halogen, -O-SO₂-CH₃, -O-SO₂-CF₃, or a moiety of the structure:



10 Z is selected from -NO₂, halogen, -CH₃ or -CF₃;
 and the pharmaceutically acceptable salts thereof.

5. A compound of Claim 1 of the formula:



15 wherein:

A is selected from -S-, -SO- or -SO₂-;

R^1 and R^2 are, independently, selected from H, C₁-C₆ alkyl or C₁-C₆
 20 perfluorinated alkyl;

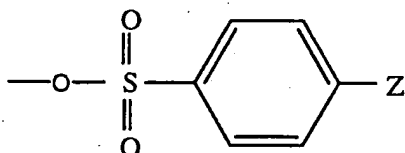
R^3 , R^4 , R^5 , and R^6 are independently selected from H, OH or the C₁-C₄ esters
 or alkyl ethers thereof, halogen, -CN, C₁-C₆ alkyl, or trifluoromethyl,

m is an integer from 0 to 3;

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R^7 and R^8 are selected independently from H, C₁-C₆ alkyl, or combined by - (CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄), -NH₃, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄), -NHCO(C₁-C₄), and -NO₂;

X is halogen, -O-SO₂-CH₃, -O-SO₂-CF₃, or a moiety of the structure:



Z is selected from -NO₂, halogen, -CH₃ or -CF₃; and the pharmaceutically acceptable salts thereof.

6. A compound of Claim 1 which is (4-Chloromethyl-phenoxy)-ethyl-piperidin-1-yl hydrochloride.

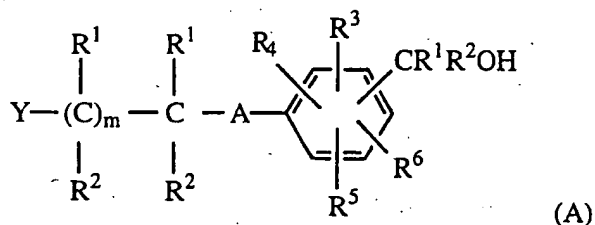
7. A compound of Claim 1 which is (4-Chloromethyl-phenoxy)-ethyl-hexamethyleneimine -1-yl hydrochloride.

8. A compound of Claim 1 which is (4-Chloromethyl-phenoxy)-ethyl-dimethylamino hydrochloride.

9. A process for preparing a compound of the formula (I) as claimed in any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, which comprises one of the following:

a) converting an alcohol of formula

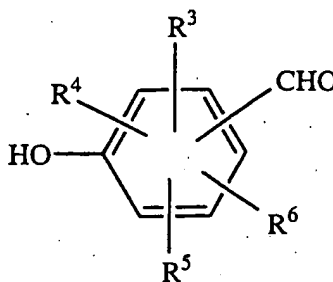
- 69 -



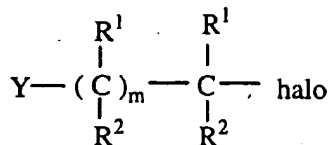
- wherein m, A, Y and R¹⁻⁶ are as defined in claim 1 to give a corresponding compound of formula (I) wherein X is a leaving group by appropriate means; e.g. using a halogenating, sulphonylating or acylating agent containing the leaving group X;
- or
- b) oxidising a compound of formula (I) wherein A is S to give a corresponding compound of formula (I) wherein A is SO or -SO₂-.
- or
- c) converting a compound of formula (I) to a pharmaceutically acceptable salt thereof.

10. A process for preparing a compound of Claim 1 wherein A is O comprising the steps of:

- a) alkylating a hydroxybenzaldehyde of the formula:

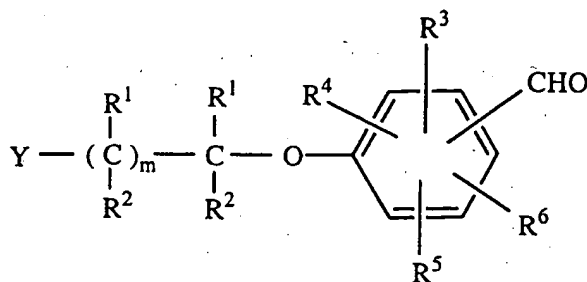


wherein R³⁻⁶ are as defined in Claim 1, with an alkyl halide of the formula:

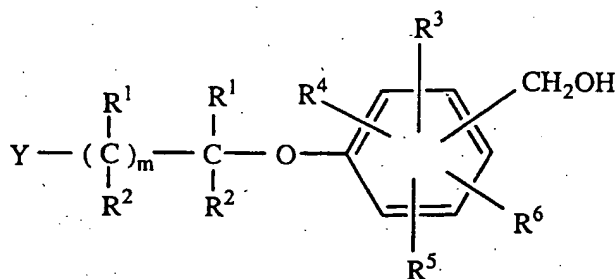


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wherein R^1 and R^2 are as defined in Claim 1, m is an integer from 0 to 3 and halo is selected Cl, F, Br or I, to produce an aldehyde of the formula:



- b) reducing the aldehyde product of step a), to yield an alcohol of the
5 formula:



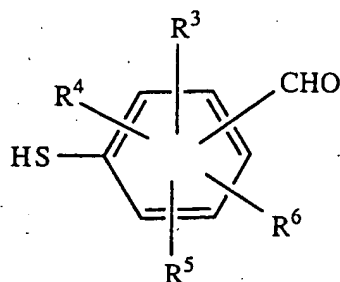
- c) converting the alcohol of step b) to its hydrochloride salt; and
d) converting the alcohol in the compound of step c) to a leaving group.

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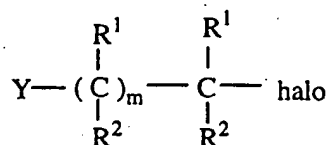
11. A process for preparing a compound of Claim 1 wherein A is S, the process comprising the steps of:

- a) alkylating a compound of the following formula:

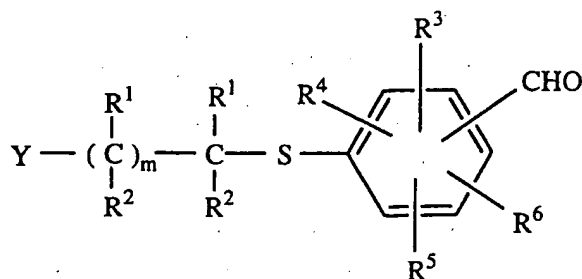
- 71 -



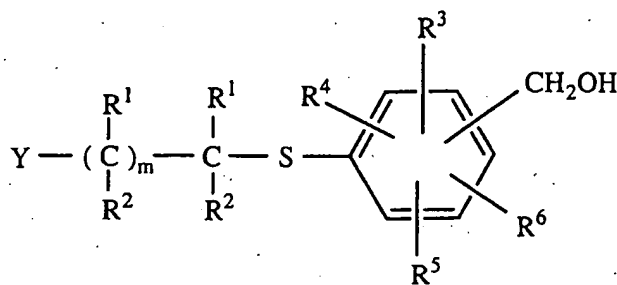
wherein R^{3-6} are as defined in claim 1 with an alkylating agent of the formula:



wherein Y, R^1 , R^2 and m are as defined in Claim 1, halo can be Cl, F, Br or I, to
 5 produce an aldehyde of the formula:



b) reduction of the aldehyde, such as with sodium borohydride, to an
 alcohol of the formula;



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c) treatment of the alcohol of step b) with gaseous HCl to generate its hydrochloride; and

d) converting the alcohol hydrochloride product of step c) to a leaving group.

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12. The process of Claim 11 further comprising the step of controlled oxidation of the sulfur in the alcohol hydrochloride of step d) to a sulfoxide or to a sulfone.

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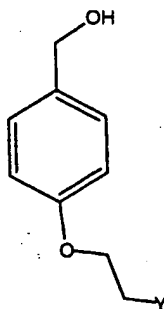
13. A process according to any one of claims 9 to 12 wherein the alcohol is converted to a leaving group through treatment with methanesulfonyl chloride, toluenesulfonyl chloride, or trifluoroacetic anhydride in the presence of pyridine or triethylamine.

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14. A process according to any one of Claims 9 to 13 wherein halo is Cl and m is 2.

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15. A process for producing compounds of the formula:

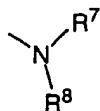


wherein Y represents:

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a) the moiety

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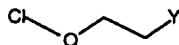


wherein R⁷ and R⁸ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl; or

- 5 b) a five-, six- or seven-membered unsaturated or partially unsaturated heterocyclic ring containing one or two nitrogen atoms, the heterocyclic ring being bound to the ethoxy bridge at a nitrogen atom in the ring and being optionally substituted by from 1 to 3 groups selected from C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ thioalkyl, -CF₃, or -NO₂;

10

the process comprising reacting, in an alkaline medium, 4-hydroxybenzyl alcohol with a salt of a compound of the formula:



- 15 wherein Y is as defined above.

16. The process of Claim 15 wherein the alkaline medium is maintained at a pH of 9 or greater.

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17. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutical acceptable salt thereof as claimed in any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/21609

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C217/48 C07D295/08 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VOJTECH KMONICEK ET AL.: "Synthesis of a Series of 5-Methyl-1H-imidazole-4-ylmethyl sulfides"	1-5,8,9, 13,14
A	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 55, 1990, pages 1602-1612, XP002093123 PRAGUE CS see page 1611; line 9 - line 30	6,7, 10-12, 15-17

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

18 February 1999

Date of mailing of the international search report

12/03/1999

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Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/21609

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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